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VOLUME 89 NUMBER 5

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

November, 1951

The Diagnosis of Carcinoma of the Pituitary Gland.
ARTHUR B. KING 339

Nerve Endings, Neurosecretory Substance and Lobular Organization of the Neurohypophysis. DAVID BODIAN 354

Changes in Blood Volume Following Operation for Pulmonic Stenosis: Studies with Evans Blue and Radioactive Phosphorus.
RICHARD C. CLAY, STUART R. ELLIOTT, II, AND H. WILLIAM SCOTT, JR. 377

Cerebral Lesions in Congenital Heart Disease. A Review of Autopsies on One Hundred and Sixty-Two Cases.
MORGAN BERTHRONG AND DAVID C. SABISTON, JR. 384

The Efficacy of Aureomycin in the Treatment of Pneumococcal Lobar Pneumonia.
R. AUSTRIAN, J. BARONDESS, G. S. MIRICK, S. M. SESSOMS, J. E. SWEENEY, AND C. G. ZUBROD 407

Book Reviews 414

PUBLISHED MONTHLY
THE JOHNS HOPKINS PRESS, Baltimore-18, Maryland
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Correspondence concerning business matters and all remittances should be sent to The Johns Hopkins Press, Baltimore-18, Maryland, U. S. A.

This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

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THE JOHNS HOPKINS PRESS
BALTIMORE-18, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Post Office. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

THE DIAGNOSIS OF CARCINOMA OF THE PITUITARY GLAND

ARTHUR B. KING*

Received for publication May 24, 1951

Among the characteristic clinical manifestations of pituitary adenomas are bitemporal defects of the visual fields, primary optic atrophy, headaches, and disturbances of growth and metabolism. An alteration of the sella turcica may be demonstrated by x-ray examination. The vast majority of neoplasms of the pituitary are benign and spread along paths of least resistance or expand the sella by pressure erosion. Since the fifth cranial nerve is separated from the pituitary gland by the bony walls of the sella, the cavernous sinus, the carotid artery and several other cranial nerves, it is rarely involved by pituitary tumors. However, there are certain cases in which pain in the face due to irritation of branches of the fifth nerve may be the presenting symptom and this type of onset is especially characteristic of a carcinomatous process arising in the gland. Under these conditions the neoplasm shows much greater powers of invasion than do the benign adenomas and the neoplasm may infiltrate for long distances before symptoms due to mass alone present themselves. The following case is offered as illustration of this statement. This patient came to the hospital with the predominant complaint of facial pain and as far as she was aware, it was her first symptom. It is considered timely that the question of facial pain with carcinoma of the pituitary be reviewed so that the proper emphasis may be placed on its significance.

CASE REPORT

L. W., White Female, Age 70 years. At the time this patient was first seen, she gave a history that three months before she had noticed a sensation of fullness in the right ear as though there was something plugging the ear canal. She had picked at the ear several times, had had others look into it, but nothing could be seen. Shortly after the onset of this sensation she began to experience pain in the right cheek. This pain spread over the maxillary area and radiated underneath the right eye and towards the nose. Soon it developed a tic-like character. The pain was described as extremely severe, knife-like and burning. It came on abruptly and frequently left almost as suddenly. It differed from tic, however, in that it would last for several minutes and she did not know of anything that would precipitate its appearance. The pain appeared spontaneously and apparently was not aggravated by washing the face, talking, eating, masticating, etc. The patient herself had not located any trigger zones. From her description one would assume the pain was primarily along the second branch of the right fifth nerve. Two or three weeks later the pain spread to involve the first division. It would appear in the eye and radiate up over the forehead and towards the ear. Until the time of examination, no pain had appeared along the mandibular branch. The discomfort in the first two divisions was becoming increasingly severe. The patient had many paroxysms each hour and was becoming hysterical about it. Approximately two

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months after the onset of the pain, she developed diplopia. Within a relatively short period of time, she noted dimness of vision of the right eye. A few days later, the right eye became completely blind. There had been no light perception in that eye during the last three weeks. Two weeks before examination she had noticed loss of smell in the right side of the nose. She could still appreciate odors on the left. At no time did she have anything suggesting uncinate fits. Although the patient realized she had lost the vision in the right eye, the reason she sought help and demanded something be done was for the intractable pain that came in ever recurring cycles over the right side of the face.

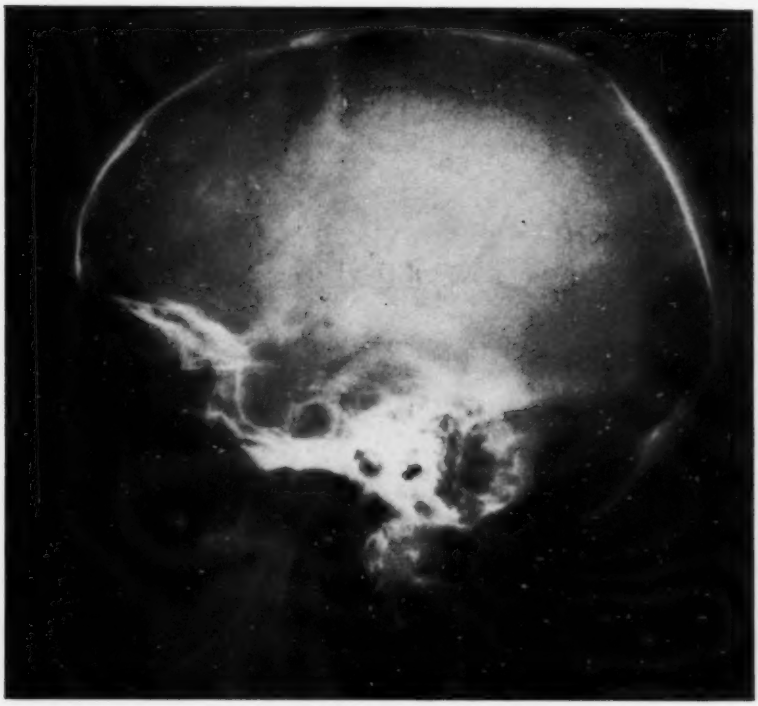

FIG. 1. Lateral x-ray of skull, showing ballooning of sella turcica, with destruction of posterior clinoids and erosion of anterior clinoid processes.

The physical examination showed a well developed and well nourished woman, who appeared somewhat younger than her stated age. She was wide awake, alert, intelligent and cooperative. Except for a blood pressure of 180/90 and mild arteriosclerosis, the physical examination showed nothing abnormal. The nose and throat consultant inspected the nasopharynx very carefully, but could detect nothing unusual. The parotid glands were normal and there were no enlarged lymph nodes in the neck.

The neurological examination disclosed anosmia on the right. On the left, the sense of smell was preserved. The right eye had no vision. On the left, vision was 20/30, and the visual field was full. The fundi of both eyes appeared normal. The blood vessels were not

remarkable and no exudates or hemorrhages were seen. There was nothing to suggest either papilledema or optic atrophy. Definite ptosis of the right lid was present but there was no proptosis of the right eye. The right pupil failed to respond both directly and consensually, to light. Almost complete impairment of movement of the right globe, both upward and inward, was noted but downward movement was still preserved. Functions of the fourth and sixth nerves appeared intact bilaterally. A definite diminution of touch and pain over the entire right side of the face was found although the loss was more marked over the first two divisions. The corneal reflex was absent on the right but active on the left. Function of the masseter and temporal muscles on the right was impaired as compared with those on the left and there was atrophy of the muscles. The remainder of the neurological examination was negative. There was nothing to suggest hormonal deficiency, such as diabetes insipidus, hypothyroidism, or excess hirsutism. Her menstrual periods had ceased many years before.

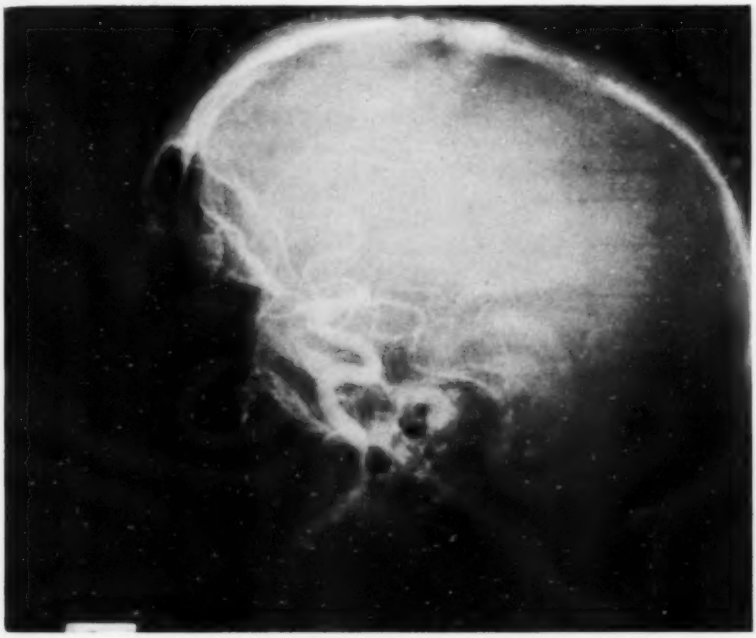

FIG. 2. Arteriogram of right internal carotid artery showing elevation of terminal portion.

Laboratory studies: The urine was normal. The hemoglobin, red cell count, white cell count and differential count were not remarkable. The blood urea was 16 mg. %; blood sugar 126 mg. %; and the Wassermann reaction negative. The spinal fluid pressure was 120 mm. of fluid and on examination it contained 6 lymphocytes per cubic millimeter. The protein was 106 mg. %.

X-rays of the chest were not remarkable. X-rays of the skull, however, showed marked changes about the sella turcica. There was almost complete destruction of the posterior

clinoids. The limits of the sella turcica were ill defined with an almost complete loss of the floor. The anterior clinoid on the right had disappeared. The floor of the right middle fossa was less radio-opaque than that on the left, suggesting destruction of the bone. There was a soft tissue mass in the sphenoid sinus and in the right ethmoid sinuses. It was also thought that there might be a soft tissue mass in the nasopharynx although this could not be seen when the nasopharynx was examined (Fig. 1).

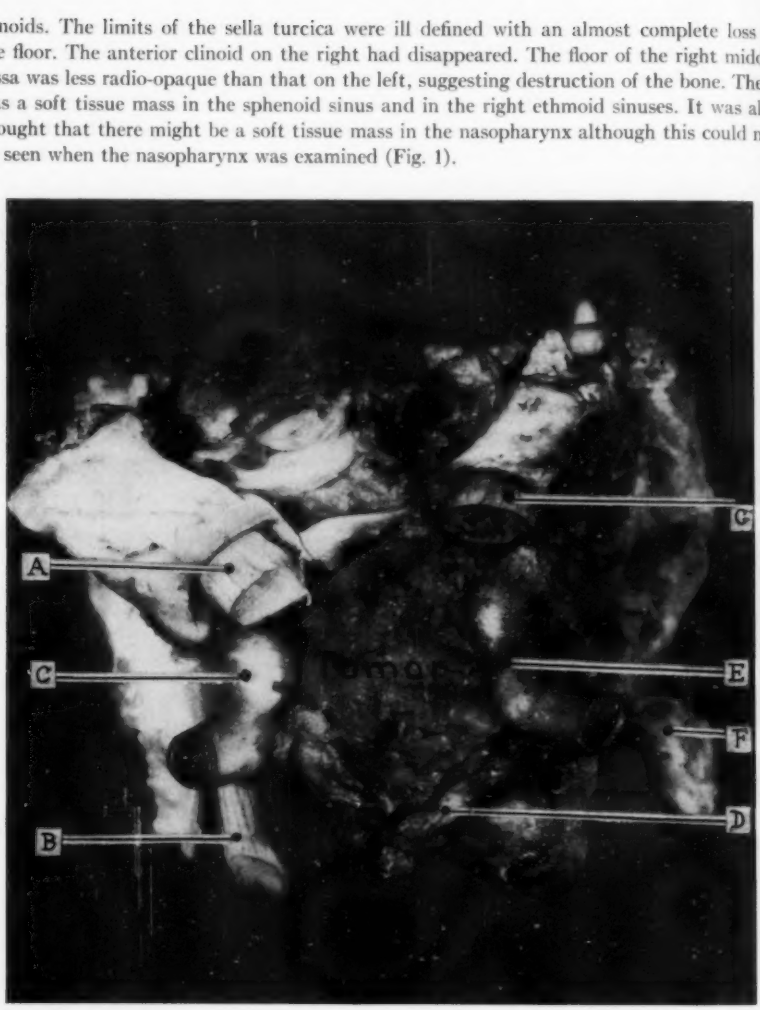

FIG. 3. View from above, the tumor is seen projecting between the carotid arteries and invading the right cavernous sinus; (a) left optic nerve, (b) left third nerve, (c) left carotid artery, (d) right third nerve, (e) right carotid artery, (f) right fifth nerve, (g) right optic nerve.

A right carotid arteriogram was done by the percutaneous method. The right middle cerebral artery was depressed near its origin from the carotid. However, the intracranial portion of the carotid artery appeared lifted upward and tilted backward. There was no gross displacement, however, and the findings were minimal (Fig. 2).

Following this procedure, a right craniotomy was done. A huge infiltrating tumor was

found in the region of the chiasm. As the chiasm was approached, the neoplasm was found invading the sphenoid wing where it had eroded the bone about the optic foramen. The tumor itself was both intra-dural and extra-dural. It was found bending the right optic nerve acutely as it entered the optic foramen. The tumor was soft, grayish, necrotic and easily aspirated with the sucker. When the nerve was decompressed, the sella could be entered and much of the tumor was removed. It was found, however, that the floor of the sella turcica had disappeared and that the sucker passed directly into the sphenoid sinus. It was also found that the tumor had eroded into the cavernous sinus and obliterated all

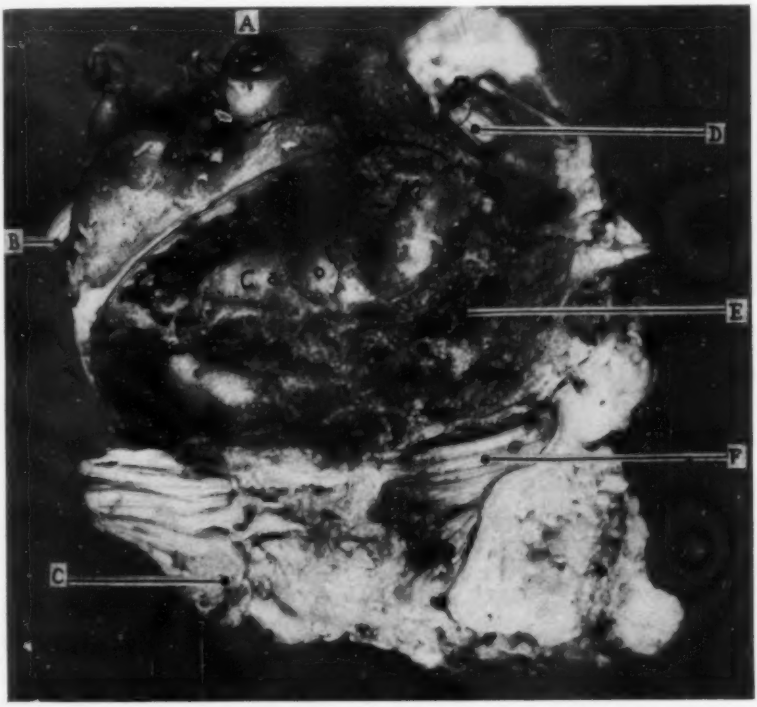

FIG. 4. View of right cavernous sinus; (a) right carotid artery, (b) right third nerve, (c) cancer in Gasserian ganglion, (d) right optic nerve, (e) tumor obliterating cavernous sinus, (f) maxillary division of right fifth nerve.

the venous spaces. Because of this, it was easy to dissect the cavernous sinus and expose the carotid artery. The walls of the artery were very soft and two small holes were accidentally produced in the artery in an effort to strip away the dura. The tumor had invaded through the cavernous sinus and into the Gasserian ganglion. The first and second divisions of the fifth nerve were infiltrated by the tumor as well as the ganglion itself. Part of the ganglion was removed together with the first two branches. An effort was made to remove the ganglion completely but because of profuse bleeding, it was necessary to terminate the operation. The bleeding apparently arose from the petrosal sinus.

The postoperative course was very stormy. While the patient awoke in the first few hours and was able to speak, her course following this was one of continual decline. On the following day she became confused and later stuporous. The wound was re-opened and it was found that she had sustained a thrombosis of the right middle cerebral artery. Despite supportive therapy, the course continued downhill and she died seven days after the operation.

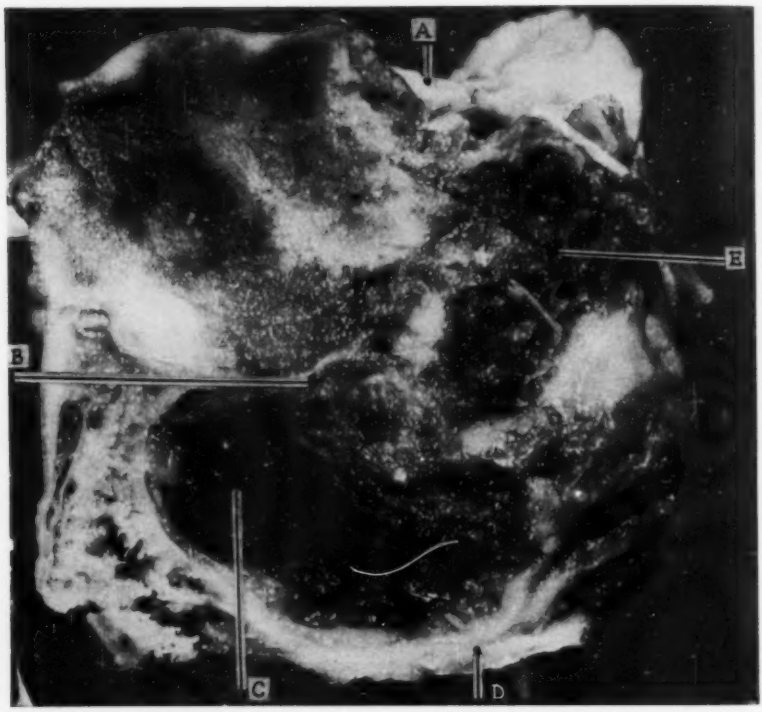

FIG. 5. Saggital section through sella turcica and sphenoid sinus, showing the neoplasm obliterating all the structures; (a) left optic nerve, (b) remanants of floor of sella, (c) tumor and hemorrhage in sphenoid sinus, (d) intact floor of sphenoid sinus, (e) tumor in ethmoid sinus.

At post mortem examination, it was clear that only a small portion of the tumor had been removed and that it was very extensive as shown by the accompanying illustrations (Figs. 3, 4, 5 and 6). The sella turcica and sphenoid sinus were removed "en bloc." Later, detailed dissection was carried out as will be described below. After the brain had been hardened, it was sectioned and no abnormality except softening due to thrombosis of the right middle cerebral artery was noted. There was no invasion of the brain by the pituitary tumor.

Microscopic sections of the neoplasm, both from operation and autopsy, showed an invasive cancer that readily invaded bone, mucous membrane and nerves. The cells were

anaplastic although in areas one could make out clusters of cells that were typical of a pituitary adenoma (Fig. 7). In other areas, however, the cells were large with three and four nuclei. The cytoplasm was well outlined and very abundant. The nuclei were large and the nuclear material stained darkly. An occasional mitotic figure was seen. The cytoplasm was not granular nor did it contain any material which could be identified as granules usually seen in cells of the chromophil variety of pituitary tumors (Fig. 8). In most areas, the pattern was very irregular with broad sheets and some tendency to condense around blood vessels.

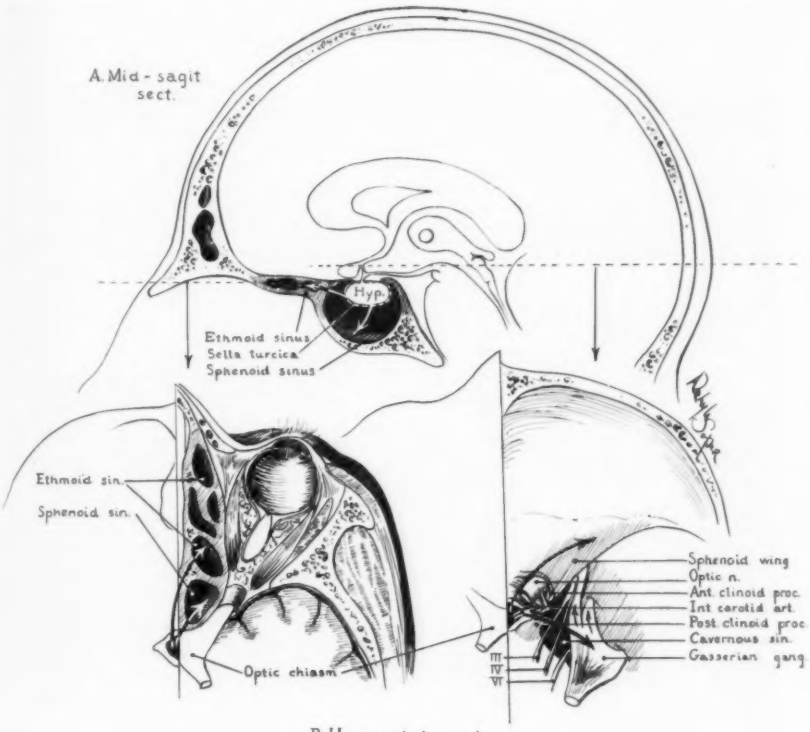

FIG. 6. Drawing illustrates extension of neoplasm into structures about the hypophysis. Invaded bone is indicated by shading. The right optic, oculomotor, trochlear and abducens nerves were surrounded and compressed by tumor tissue. The trigeminal nerve and Gasserian ganglion were actually infiltrated by the cancer (compare with Fig. 4).

There were many blood vessels throughout the tumor but these did not appear abnormal. Sections of the carotid artery showed the tumor invading the adventitia. The entire cavernous sinus was filled with soft grayish neoplasm. The Gasserian ganglion, the root and all the branches of the fifth nerve were penetrated by tumor masses and individual axones were frequently separated by clusters of tumor cells. From the characteristics of the tumor, there seemed to be little doubt that this was a carcinoma of at least moderate malignancy arising in the pituitary gland.

CRITERIA FOR DIAGNOSIS OF CARCINOMA OF THE PITUITARY

Despite considerable work done by many authors on the classification of the pituitary neoplasms, there is still no definite agreement as to what constitutes a carcinoma of the pituitary gland. If the criterion is to be based solely on the presence of metastases, then carcinomata of the pituitary are extraordinarily rare. Jefferson, describing very large pituitary tumors with intracranial extensions, felt that metastases were necessary in order to make the diagnosis of carcinoma. In discussing his own cases, he felt that none met

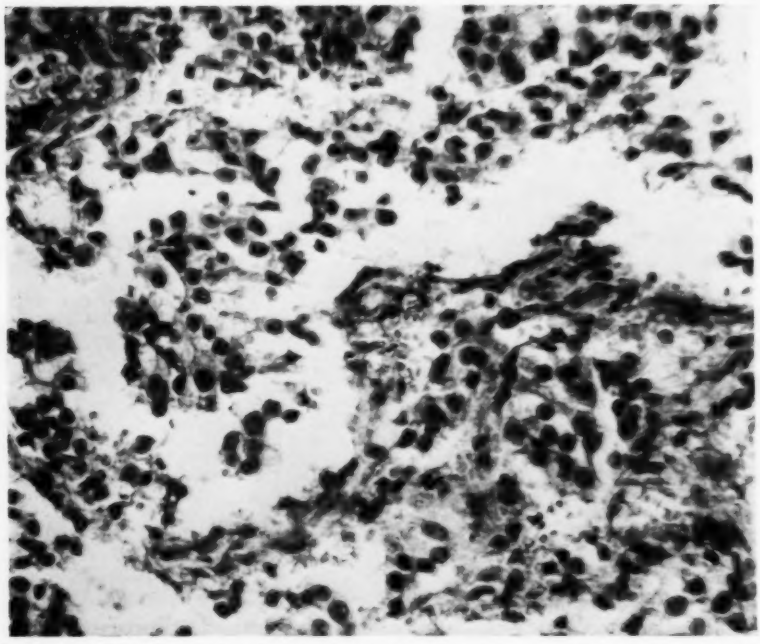

FIG. 7. Section of tumor showing arrangement similar to an ordinary pituitary adenoma.

this criterion. While many of his tumors were extremely extensive, they were still within their capsule and had eroded surrounding structures by pressure only. Bailey and Cutler, who critically reviewed much of the published material, feel that perhaps in none of the cases was evidence sufficient to warrant a categorical statement that the neoplasm in question was a pituitary carcinoma with metastases. On the other hand, Krause, who uses somewhat different criteria, or should it be said is less rigid, states that carcinoma of the pituitary is relatively frequent. He cautions, however, that metastases are extremely rare. He feels that several of the so-called "malignant adenomas"

which show extensive local infiltration, are probably carcinomas. Beside infiltration, he mentions that the cells may show marked anaplasia, irregularity of size and shape, particularly of the nuclei. These cells contain large nuclei with dark staining nuclear material; they lose their alveolar arrangement and form very dense masses of cells. All this tends to make the diagnosis of pituitary carcinoma probable. Usually the specific cell granules are not present

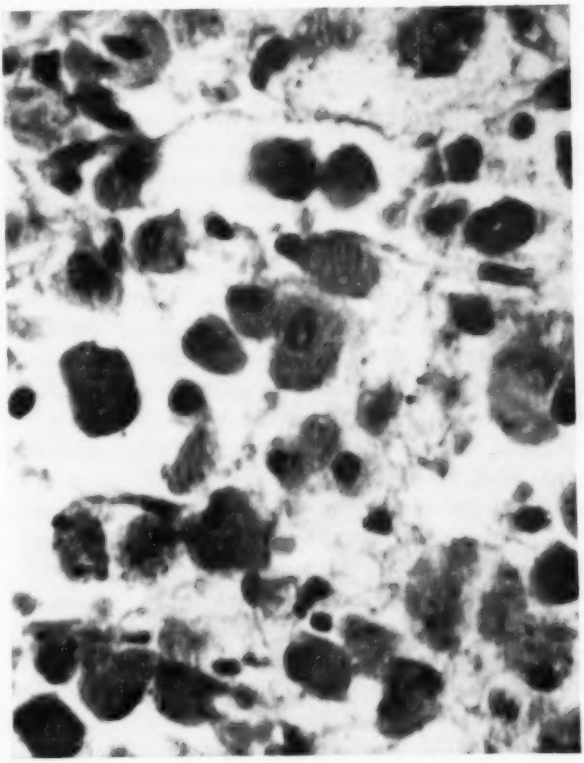

FIG. 8. Section showing large anaplastic "malignant" cells (oil emersion). The small dark spots which look like granules are staining artifacts.

and the cells may be so anaplastic that it is almost impossible to determine with certainty from which cell type the tumor arose. Hence, the usual criteria of a malignant neoplasm, i.e., mitoses, anaplasia, loss of functional arrangement, and marked invasion of the surrounding tissues seem to be applicable to the grading of the malignancy of pituitary tumors.

Weinberger, Adler and Grant reported several cases in which the cavernous sinus was invaded by cells outside a definite capsule and in which the cellular

elements were also found in bone and nerve. They merely designated these tumors as "cellular adenomas." Bailey and Cutler, reviewing Cushing's series of tumors, found three that had eroded bone or invaded nerves. They preferred the term "malignant adenoma," comparing these tumors to meningiomas and neurofibromas which show local invasion but fail to metastasize.

It is my feeling that to demand the presence of metastases in order to establish the diagnosis of malignancy is too narrow a definition and I feel that the criteria set down by Krause are sufficient to warrant the diagnosis of carcinoma of the pituitary gland. Even under these conditions the incidence of carcinoma is low. Should it be assumed that the cases described by Bailey and Cutler fulfill these criteria, there are only three in the entire Cushing series. Of the 169 cases studied by Weinberger, et al. perhaps five or six may be called carcinoma. Walsh, in reviewing 50 cases of pituitary tumors from the Johns Hopkins Hospital series, describes four carcinomas. This incidence is somewhat higher than other series and it is likely that the requirements as outlined by Krause were not as rigidly followed. In a large series of tumors available to Keyes, Lee and Stout, three had invaded the nasal cavity. They felt that these tumors had perforated into the sinuses by direct extension and while they showed all the characteristics of carcinoma, they were unwilling to label the tumors as such because of the lack of metastases. It need only be mentioned in passing that all the neoplasms arose from the glandular elements of the pituitary and that no tumors that could be classified as carcinoma developed from the pars nervosa. Since the anterior portion of the gland is derived from tissue originating in the roof of the mouth, it is difficult to understand why carcinoma should be such a rarity, since cancers of other structures in the oral cavity are so common.

The mode of spread of pituitary tumors beyond the sella turcica has been extensively studied. The year 1940 saw two interesting and detailed studies on this point; one carried out by Weinberger et al. and the other by Jefferson. In 1942, White described the spread of a huge pituitary tumor which invaded far into the middle fossa. Walsh, in describing two cases of bilateral total ophthalmoplegia, illustrated the possible modes of extension of pituitary tumors with the most detailed and illuminating illustrations. These should be consulted to fully understand the anatomy, both of spread and the structures involved when a pituitary tumor escapes from the confines of the sella turcica.

A comparison of the process of extension of adenomas with that of carcinoma, shows that adenomas appear to take the course of least resistance. They usually project between the optic nerves. Once they have gained the region of the chiasmal cistern, they may invade the base of the third ventricle or push into the anterior fossa. When the tumors become very large they may extend by pressure erosion into the paranasal sinuses, or into the middle fossa. From a purely mechanical point of view, one would feel that direct invasion

through all the structures of the cavernous sinus into the fifth nerve ganglion would be most difficult and would require the greatest pressure over the longest period of time. This probably accounts for the infrequency with which facial pain is encountered with adenomata. On the other hand, invasive tumors that are able to destroy surrounding structures with ease, readily penetrate directly though the cavernous sinus or into the sphenoid and ethmoid sinuses. They frequently do so before growing into a sizable intracranial mass.

THE ROLE OF FACIAL PAIN WITH MALIGNANT PITUITARY GROWTHS

Foix was one of the first observers who called attention to the presence of facial pain in benign pituitary adenomas. However, the presence of facial pain with pituitary neoplasm is sometimes stated as being one of the criteria of malignancy. This was pointed out by Jefferson, who mentions that trigeminal anesthesia is a definite sign that the tumor has invaded the cavernous sinus. He mentions that sensory changes in all three divisions indicate invasion of Meckel's cave and probably the sensory root. Pain in the face should definitely be considered as due to cancer. In one of the cases reported by him in which there was a large adenoma, there had been erosion of the cavernous sinus and direct impingement upon the fifth nerve producing facial anesthesia. Weinberger, et al., had six patients who complained of facial pain. All of these cases had pronounced invasion of the cavernous sinus. One of the tumors reported by Bailey and Cutler had invaded the Gasserian ganglion and some of the branches of the fifth nerve. This was demonstrated by microscopic study. This patient, however, did not have pain, which seems peculiar. Walsh, in his series, had no patients with facial pain although the corneal reflex was lost in one.

A benign adenoma exerting pressure on the fifth nerve, will often cause loss of function shown by the hypesthesia, anesthesia, and a diminished corneal reflex before it produces pain. On the other hand, infiltration of the nerve by carcinoma cells, will directly irritate and damage it, thus producing pain early, even before loss of function can be detected. This is characteristic of cancer. While these two types of action are not absolute, they are often most helpful in arriving at a clinical diagnosis.

The Gasserian ganglion and the branches of the fifth nerve are located laterally and only a large pituitary tumor can impinge on them directly by pressure, and push aside many structures, including the third, fourth and sixth nerves, together with the vascular structures of the cavernous sinus. Walsh pointed out that while his cases had complete ophthalmoplegia and one had total blindness, there was preservation of the fifth nerve function. He suggested that it was due to pressure. As motor nerves are more sensitive to pressure than sensory nerves, conduction was blocked while the sensory

components of the fifth nerve were still able to transmit impulses and therefore there was neither anesthesia nor pain. He postulated, also, that the sudden loss of vision could be either due to hemorrhage, which is one of the most common complications of pituitary tumors, as has been recently emphasized by Brougham, et al., or due to other causes producing a sudden swelling of the neoplasm and thereby acute pressure on the optic nerves.

COMMENT ON THE CASE PRESENTATION

The situation in the case cited is quite different. Here the tumor had great invasive powers and there was no trace of a capsule. It had not only invaded and obliterated the right cavernous sinus, but actually invaded the walls of the carotid artery. It had encroached into the paranasal sinuses, had destroyed their bony walls and infiltrated bone of the sphenoid wing. Small tumor masses had penetrated beyond the cavernous sinus and had invaded the branches of the fifth nerve and the Gasserian ganglion. We have evidence that this tumor irritated the fifth nerve, and produced pain long before visual disturbances. This is characteristic of carcinoma and a most unusual behavior for a benign adenoma. Study of the accompanying photographs will show that despite the large size of the tumor, it apparently surrounded the nerves of the cavernous sinus and did not exert sufficient pressure upon them to produce paralysis.

The remaining neurological findings are easily explained by the extension of the tumor. Anosmia was due to invasion of the sinuses rather than involvement of the first cranial nerve. The visual loss came on rapidly and was complete while the optic nerve head appeared normal. This would suggest either a rapid compression of the optic nerve due to hemorrhage or swelling within the tumor, or an interruption of the blood supply of the nerve. A small hemorrhage deep inside the tumor was found at autopsy but since the neoplasm was so soft, I would suspect that the sudden loss of vision was probably due to occlusion of nutrient arteries rather than to direct pressure on the optic nerve. While the optic nerve was elevated and somewhat angulated, it was not thin and atrophic which is the usual appearance produced by a pituitary adenoma, where the visual loss and optic atrophy are produced over a long period of time. The third, fourth and sixth nerves were surrounded by tumor throughout the length of the cavernous sinus as well as in the region of a superior orbital fissure. However, there was only partial loss of the third nerve function and the eye movements controlled by the fourth and sixth nerves were intact. The pressure produced by the tumor must have been so mild that they were able to function almost normally. On the other hand, the first and second branches of the fifth nerve and the Gasserian ganglion were actually invaded by gross masses of tumor tissue. This produced not only the loss of corneal reflex and almost complete anesthesia, but also produced pain.

DIFFERENTIAL DIAGNOSIS OF FACIAL PAIN

Besides sinus disease, carious teeth, tic douloureux and the atypical neuralgias, facial pain may be produced by aneurysms, benign pituitary tumors, chordomas, an occasional acoustic neuroma, and tumors of the Gasserian ganglion. Much more common, however, are carcinomata of the naso-pharynx, which invade the middle fossa and involve one or more branches of the fifth nerve. Recently, I have had some experience with unusual parotid carcinomata which have also invaded the middle fossa and produced typical facial discomfort which one associates with malignant nasopharyngeal neoplasms. Marked bony destruction of the middle fossa, floor of the sella and masses in the sphenoid and ethmoid sinuses led me to believe that the patient under discussion had a chordoma rather than a large pituitary tumor. However, I know of no absolute finding which could distinguish the two, other than microscopic study. The arteriogram effectively ruled out an aneurysm and a large intracranial neoplasm. It suggested that the neoplasm was invasive, surrounding the carotid siphon rather than displacing it. Nose and throat examination seemed to rule out a nasopharyngeal carcinoma.

TREATMENT OF PITUITARY CARCINOMA

Treatment of carcinoma of the pituitary is still far from standardized. Since the condition cannot be diagnosed save by microscopic study of the neoplasm, an adequate biopsy would appear to be the first prerequisite. Since many types of tumors may arise in the neighborhood of the sella and frequently they are not sensitive to radiation therapy, it is not surprising that many of the published reports are contradictory concerning the value of x-rays on pituitary carcinomas which were irradiated without adequate microscopic confirmation.

Craniotomy to decompress the optic nerves and adjacent structures should be carried out. Then intensive x-ray therapy may be applied after the tumor has been found to be of pituitary origin. In my limited experience with both extensive adenomas and pituitary neoplasm considered to be carcinomas, the results have been only temporarily palliative. Unfortunately, surgery alone will not cure them.

In the foregoing case, operative treatment was directed along two ways; one was an attempt to decompress the right optic nerve, hoping that vision might return, and the other was section of the fifth nerve to alleviate pain. Obviously the neoplasm was too large for complete surgical removal. Unfortunately, the operative approach required to decompress the second nerve and to cut the fifth at the same sitting is quite extensive and, in this instance, was not tolerated by the patient. It would perhaps have been wiser to have confined the operative procedure to sectioning the fifth nerve to relieve pain and securing a biopsy, then depending upon radiation therapy to control

the neoplasm. It has been my experience that x-ray therapy will never permanently relieve pain if the fifth nerve is actually invaded by a neoplasm of any type.

CONCLUSIONS

It is my feeling that the neoplasm described above is a carcinoma of the pituitary gland. The widespread invasion by the neoplasm with disregard for the usual anatomical barriers; the absence of any capsule; the histological picture of the individual cells and the rapid progression of symptoms, all make the diagnosis almost inescapable. The only factor missing is that of metastases. Since it is not known how large a cancer has to be before it metastasizes, and at what period in its life history this occurs, it seems to me it is an unduly rigid qualification to insist on their presence. Certainly carcinomata are recognized elsewhere in the body without metastases. In bulk, a pituitary tumor which produces clinical symptoms is actually quite small compared to symptomatic carcinomata elsewhere. It is not unusual to remove carcinoma of the breast or bowel of much larger size and find no metastases. It is quite possible that patients with cancer of the pituitary succumb to the intracranial complications before they have lived long enough to develop metastases.

The presence of facial pain, along with clinical and x-ray evidence of a pituitary tumor, strongly suggests that the neoplasm is a carcinoma. This is especially true when it is an early manifestation, because a benign adenoma usually extends in directions other than through the cavernous sinus, while a highly invasive neoplasm may reach the fifth nerve by destruction and penetration of the surrounding structures while exerting less pressure on the other cranial nerves to cause loss of function. The size and extent of the tumor in the patient described above illustrates how the motor nerves in the cavernous sinus were only mildly affected, while the irritation of the sensory components of the fifth nerve resulted in the principal complaint of facial pain.

SUMMARY

A case of carcinoma of the pituitary gland in which facial pain was the predominant symptom has been described. The difficulty in diagnosing a carcinoma arising from the pituitary gland is discussed. The importance of facial pain produced by a pituitary neoplasm in the evaluation of the type and spread of the tumor is emphasized.

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NERVE ENDINGS, NEUROSECRETORY SUBSTANCE AND LOBULAR ORGANIZATION OF THE NEUROHYPOPHYSIS

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Received for publication August 2, 1951

The neural lobe of the hypophysis is known to be one of the most richly innervated of all glandular structures, yet this important gland, which is essential for the regulation of water balance, is one in which no logical relationship between structure and function has been demonstrated. The description of this organ as a "tangle of nerve fibers and neuroglia cells" by one despairing observer, neatly sums up the feeling of defeat which most histologists have felt who have examined sections or descriptions of sections of the pars nervosa. An exhaustive study by Romeis, published in Möllendorff's handbook (1940), introduced some order into the analysis of the pars nervosa, but did not elucidate its fundamental plan. As so often happens in biology, however, the species of animal selected for a study of a particular problem may be an important factor in its clarification. Although a vague sort of lobulation is suggested in the pars nervosa of many vertebrate species, and has been commented upon by a number of authors, no clear structural plan has been formulated in any of the descriptions that have come to our attention. Romeis (1940) expresses succinctly the principal difficulty when he states that although one gets the impression of lobulation in the human pars nervosa, with dense zones and less dense "Zwischenstreifen," nowhere can one distinguish a sharp border formed by the connective tissue septa. Although the contrast between the "Verdichtungszonen" and "Zwischenzonen" is clearly revealed by maceration, by differences in vascularity, by differences in density of cell nuclei, and by differences in nerve fiber content, the zones are poorly demarcated and the trabecular arrangement of blood vessels and surrounding connective tissue seems more haphazard than orderly in most species.

The present account can add little to the descriptions of the individual cellular elements of the pars nervosa by Bucy (1930) and by Romeis (1940), but clarifies for the first time the mode of termination of nerve fibers in this structure. Because it is primarily based on the hypophysis of the opossum, in which an orderly and intelligible histological architecture can be seen almost at a glance in appropriately stained sections, it was thought that it might serve to clarify the organization of these elements in other vertebrates as well.

MATERIALS AND METHODS

Mature animals of two species were used in this investigation. The opossum (Didelphis virginiana) was the principal contributor; the rheusus monkey (Macaca mulatta) served

as a representative of most other species of mammals, including man, in which the simple and probably primitive organization is distorted into a less easily understood pattern. All material was fixed by arterial perfusion of the anesthetized animal as previously described (Bodian, 1936), and was embedded in paraffin. Fixatives used are listed below, in company with the staining methods employed in each instance:

Maximow's fixative or *formol-Zenker* (Mallory-Heidenhain azan; method of Gomori, 1941).

Bouin (Gomori method).

Acidified formalin and *10% formol in normal saline* (Protargol—Bodian, 1936, 1937).

Huber's fixative (1927—3% $HgCl_2$, 1.5% trichloracetic acid, in 95% ethyl alcohol): (Protargol, counterstained with azan).

Best results were obtained by perfusing fixatives through the heads of anesthetized animals. The best fixative for the Gomori and the Mallory methods was Maximow's osmic-formol-Zenker, and the best fixatives for the protargol stain were Huber's fluid and formol-saline.

GENERAL STRUCTURAL PLAN OF THE PARS NERVOSA OF THE OPOSSUM

The pars nervosa of the opossum, in sections stained to show connective tissue, is readily observed to be lobulated in a rather regular fashion by septa which extend inward from the leptomeninges, and which contain the blood vessels (Figure 1). This distinct lobulation was indicated in passing in an earlier study (Bodian, 1939, Figure 7), but apparently has escaped general notice, or at least has not been mentioned in studies of the general morphological histology of the opossum pituitary (Dawson, 1938; Wheeler, 1943; Green, 1951). In the central part of the gland, the lobules are less well defined than in the periphery, where their concentric arrangement is often quite regular. In reduced silver preparations, however, in which both nerve fibers and the cell nuclei of the connective tissue septa are well stained, the lobular structure of the pars nervosa is most strikingly shown (Figure 2).

The septal zone. The septal zone, which constitutes the connective tissue skeleton of the pars nervosa, outlines the gland itself, and its lobules, and continues in the depths of the gland as delicate trabeculae (Figures 1 and 2). Throughout, it contains the blood vessels of the pars nervosa, but in addition it shows some additional features which bear on one of the most elusive aspects of the structure of the pars nervosa, especially in other mammals. In certain parts of the gland, especially at its periphery, the septal zone appears to split so as to form lobule-like islands (Figures 3 and 4—acc.). These islands, however, although they resemble superficially the true lobules of the gland, in ordinary preparations, are seen in azan material to consist largely of the endings of nerve fibers and pituicytes which project into the interstices of the septal zone, and of large masses of a substance, first described by Herring (1908, 1913) in many vertebrate species, and shown by Bargmann (1949) to be selectively stainable by the chrom-alum hematoxylin method of Gomori (1941). We shall refer hereafter to this substance as the "neurosecretory substance." It would seem that

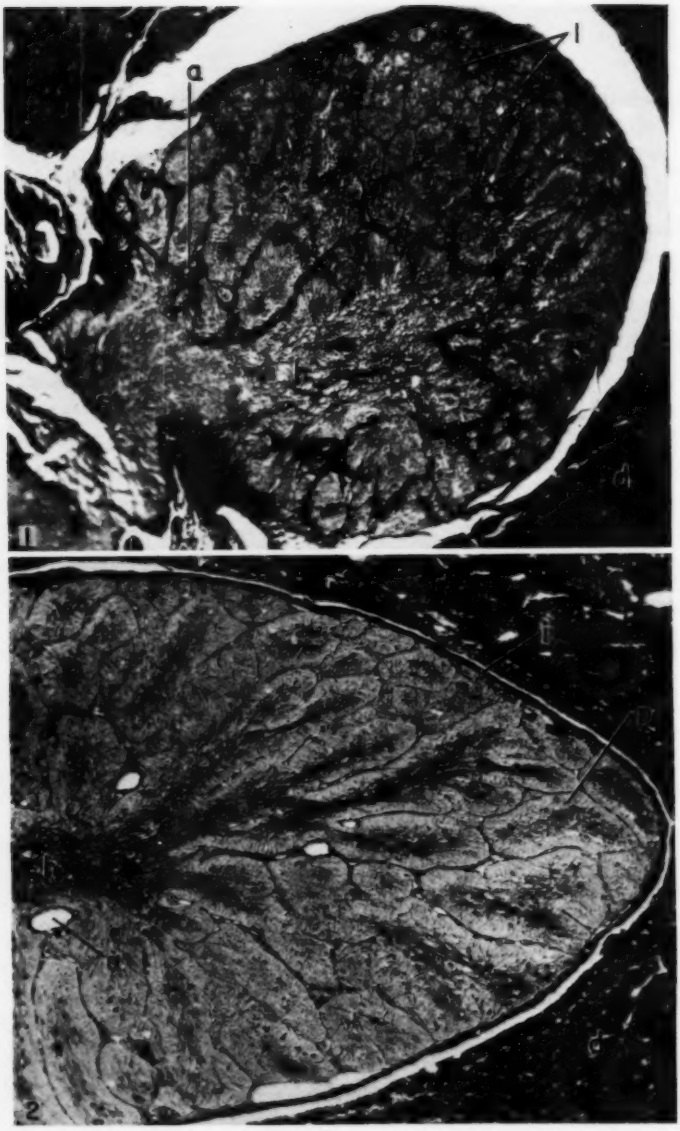


FIG. 1. Neural lobe of opossum. Lobules are circumscribed by vascular connective tissue septa. a—large artery penetrating the neural lobe from the region of the stalk. d—pars distalis, separated by a cleft from the pars intermedia. h—hilum of neural lobe, consisting of hypothalamo-hypophysial tract. l—lobules. st—stalk, containing infundibular recess. Mallory-azan. ×70.

FIG. 2. Section similar to that in figure 1, but stained with protargol. Main artery (a) and other vessels are clearly shown in the interlobular septa because of perfusion of fixative. d—pars distalis. h—hilum. i—pars intermedia. p—palisade layer of a lobule, containing very few pituicyte nuclei. ×70.

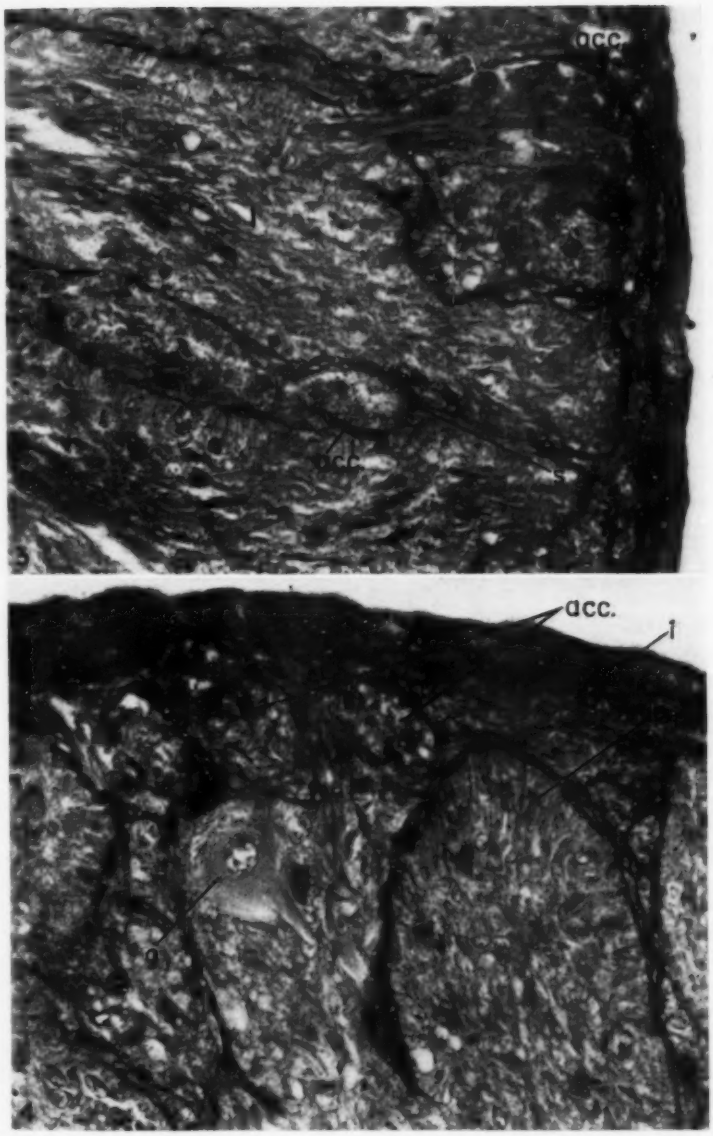


FIG. 3. Primary lobule (1) of opossum neural lobe with formation of accessory lobule (acc.) above by penetration of septal layer by nerve fibers and pituicyte fibers. An accessory lobule is shown below (acc.) within the interlobular septum (S). Mallory-azan. ×360.

FIG. 4. Lobules and accessory lobules (acc.) of opossum neural lobe. g—giant pituicyte in primary lobule. i—pars intermedia. p—palisade zone, showing pituicyte fibers. Nuclei of pituicytes are clustered in central hilum of this lobule. Mallory-azan. ×360.

this process of formation of accessory lobules may have been carried to such an extreme in other mammals as to obscure the relatively simple structural pattern observed in the opossum.

The hilum. The hilum or core of the pars nervosa lobule is composed primarily of a bundle of unmyelinated nerve fibers derived from the hypothalamo-hypophysial tract. This tract forms the hilum of the pars nervosa itself (Figure 5, tr), and each branch which enters and forms the hilum of a lobule repeats, more or less, the structure of the tract itself (Figure 6, f). The hilum also contains most of the nucleated portions of the pituicytes (Figure 7, pit.) as well as large masses of intercellular material which stains with the Gomori method (1941), whether discrete bodies (Herring bodies) or diffusely distributed material (neurosecretory substance) (Figure 8, HB and Hs). Of special interest and importance is the fact revealed by Bargmann's studies, namely that this material, which is selectively stained by the Gomori method, is also present in or on the cells of the paraventricular and supraoptic nuclei, and along the entire length of their axons, into the pars nervosa in vertebrates. It is clear from his illustrations that the form of the dendrites of these nerve cells is also outlined in the brain.

The nerve fibers of the hilum not only may be outlined by the Gomori stain (Figure 8, ax) because of the associated neurosecretory substance, but are separated by large masses of this material in interfibrillary spaces. After fixation in formol, which does not preserve this material well, these spaces containing the Herring substance give the hilum a characteristically sievelike appearance.

The palisade zone. Between the septal zone and the hilum of each lobule, in ordinary histological preparations, is a layer which has a rather homogeneous appearance, somewhat like the molecular layers of the cerebral or cerebellar cortex (Figures 2, 4, 6—p). This layer is probably the "Zwischenzone" of Romeis (1940) and is also illustrated by Green (1951) in several mammals, including the opossum, with little discussion as to its significance, except that it is traversed by nerve fibers which terminate in relation to the vascular net. His preparations with protargol show the general aspect of this layer but seem to be incompletely impregnated, as are some of ours. Our best preparations, however, show that in this relatively cell-body-free layer the nerve fibers of the hilum arborize and form a dense thicket of extremely fine, rod-like endings (Figures 9, 10, 12, 15,—e). This layer also contains the cytoplasmic prolongations of the pituicytes (Figures 7, 11, 12—cp). In the palisade layer the pituicytes, which are interspersed among the nerve fiber terminals, frequently lie parallel to each other so as to give the layer an epithelioid appearance in some places (Figure 11—cp). Some of the pituicyte prolongations, like the nerve fiber arborizations, do not extend beyond the plexiform zone, but appear to terminate in relation to blood vessel walls in the septal zone or on

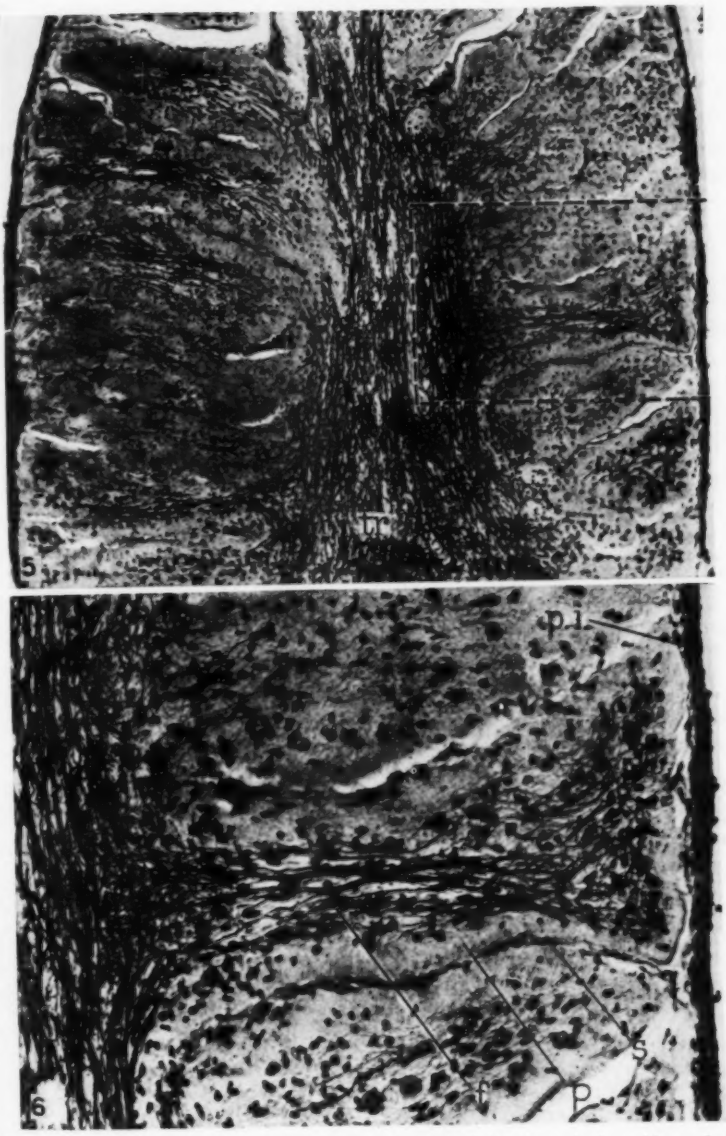


FIG. 5. Opossum neural lobe stained with protargol and showing relation of hypothalamo-hypophysial tract (tr) to lobules. ×75.

FIG. 6. Same section as shown in fig. 5, showing fibers (f) from hypothalamo-hypophysial tract entering the hilum of a lobule. p—palisade zone, poor in nuclei. s—septal layer. p.i.—pars intermedia. ×190.

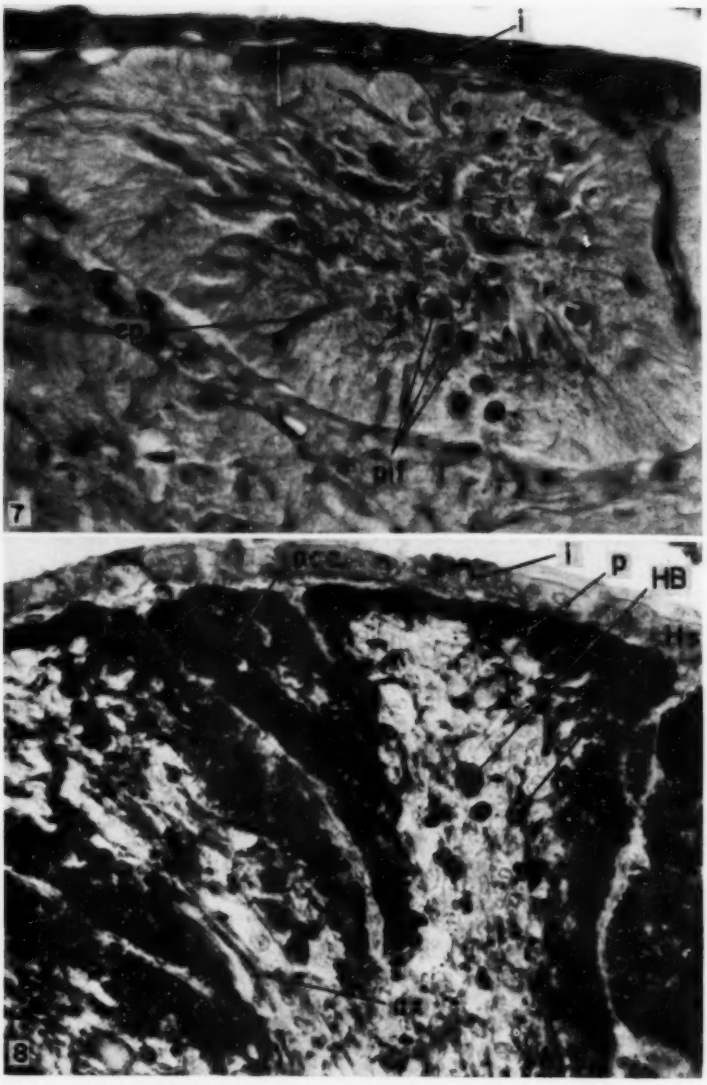


FIG. 7. A peripheral lobule of the opossum neural lobe, stained with protargol, and showing the arrangement of nerve fibers in the central hilum, interspersed with pituicyte cell bodies (pit). Surrounding the hilar zone is the palisade zone, containing the coarse cytoplasmic processes of the pituicytes (cp), and the finer, rod-like nerve endings, arranged as a palisade perpendicularly to the lobular surface. i—pars intermedia. ×470.

FIG. 8. Lobules of opossum neural lobe, stained with Gomori's hematoxylin method. The peripheral palisade zone (p) is heavily stained with hematoxylin, as are the Herring bodies (HB), diffuse masses of neurosecretory substance in the hilum (HS), and occasional nerve fibers in the hilum (ax). acc.—accesory lobule, containing very few of the unstained pituicyte cell bodies. i—pars intermedia. ×360.

collagen bundles in this layer (Bucy, 1930). Many other pituicyte prolongations, however, extend well into or through the septal layer, connecting their lobule with adjacent lobules (Figure 3). The essential feature of the palisade layer, hitherto not clearly described, is the dense and highly selective staining of this layer with the Gomori stain (Figures 8, 13, 16—p), and the arrangement of the rod-like nerve endings in the form of a regular palisade, in which pituicyte fibers are dispersed (Figures 12, 15).

This layer not only stains selectively with the Gomori stain, but careful study shows that this method stains rods which approximate in number the nerve fiber terminal rods (Figures 16, 17, 18). Pituicyte fibers, on the contrary, are stained by the phloxin and stand out in sharp contrast to the "palisade" formation of hematoxylin staining material. In the best fixed material and especially with osmic containing fixative, it can be seen that the rod-like structures stained with the Gomori method are cylinders which contain the nerve fiber terminals as a central core (Figure 16). It is interesting that in the species studied by Bargmann with this method the arrangement of Gomori-staining material was irregular and variable, except for indications of clustering near the pars intermedia. We have observed a similar distribution in the rhesus monkey (Figure 14). In this species a more complex morphology of lobules is observed since apparently the formation of accessory lobules and inversion of lobules has occurred to an extreme degree. Analysis with protargol preparations, however, has revealed typical lobules such as those seen in the opossum (Figure 20), as well as inverted lobules with septal tissue and blood vessels in the center (Figure 21). In favorable material which stains differentially both the nerve fiber terminals and the pituicyte arborizations (Huber's fixative—protargol-azan), it can also be clearly seen that the former comprise the primary elements of the palisade layer and are arranged in a manner duplicating the appearance of the rods seen in Gomori-stained sections (Figures 7, 12, 15). In all material examined, it is clear that Gomori-staining material, including Herring bodies, are primarily related to the nerve cells and nerve fibers of the hypothalamo-hypophysial system, and especially the nerve fiber endings. The morphologic relationship of the neurosecretory substance in the palisade zone to the nerve fibers and the pituicytes seems to be analogous to the relation of the myelin of nerve fibers to the axon and Schwann cells, respectively. Whether it is the pituicytes or the nerve fibers which secrete the neurosecretory substance becomes a question as difficult to answer as the question of origin of myelin, but the structural relations suggest a primary role of the nerve fibers. The architecture of the lobule of the pars nervosa of the opossum is summarized diagrammatically in Figure 22.

The Herring bodies. Our observations in the opossum pars nervosa are consistent with those of other investigators who have identified these masses with the terminal bulb formations of nerve fibers of the hypothalamo-hypo-

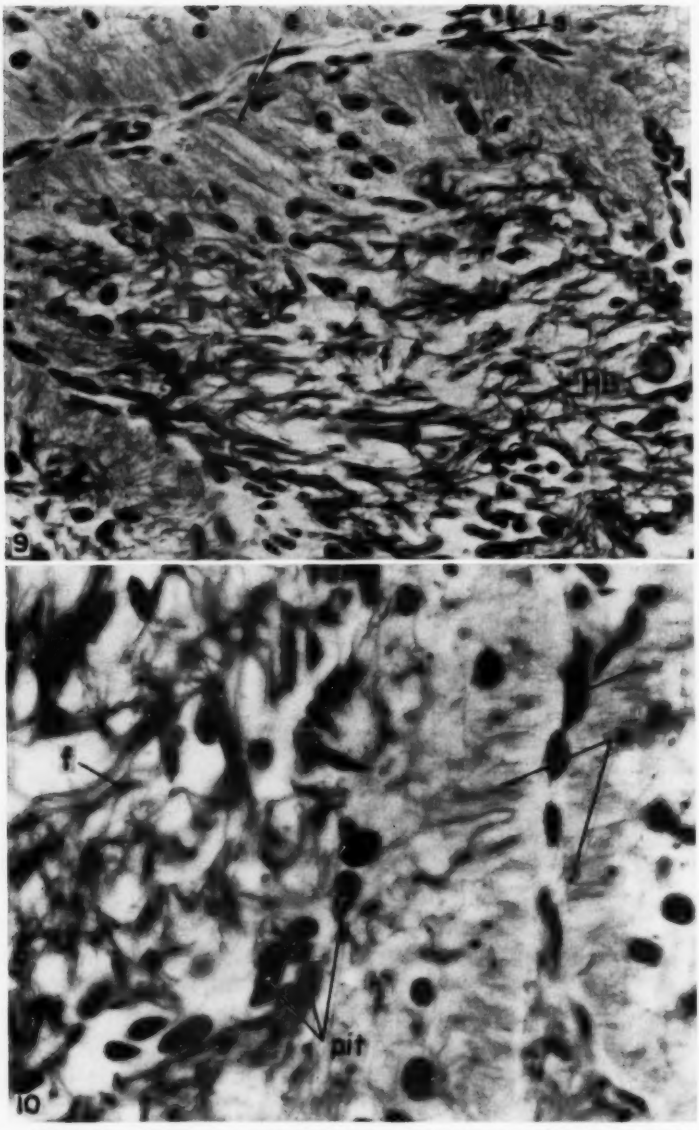


FIG. 9. Lobule of opossum neural lobe, stained with protargol. The relatively coarse fibers of the hypothalamo-hypophysial tract (f) are shown in the central hilum, and their finer terminal arborizations are shown in the peripheral palisade zone (e). s—collagenous septal zone. HB—Herring body. ×360.

FIG. 10. Same section as in fig. 9, at higher magnification. Note that some of the terminals of the hypothalamo-hypophysial tract fibers (f), form loops in the palisade layer (e). pit—pituicyte nuclei. s—septal layer. ×690.

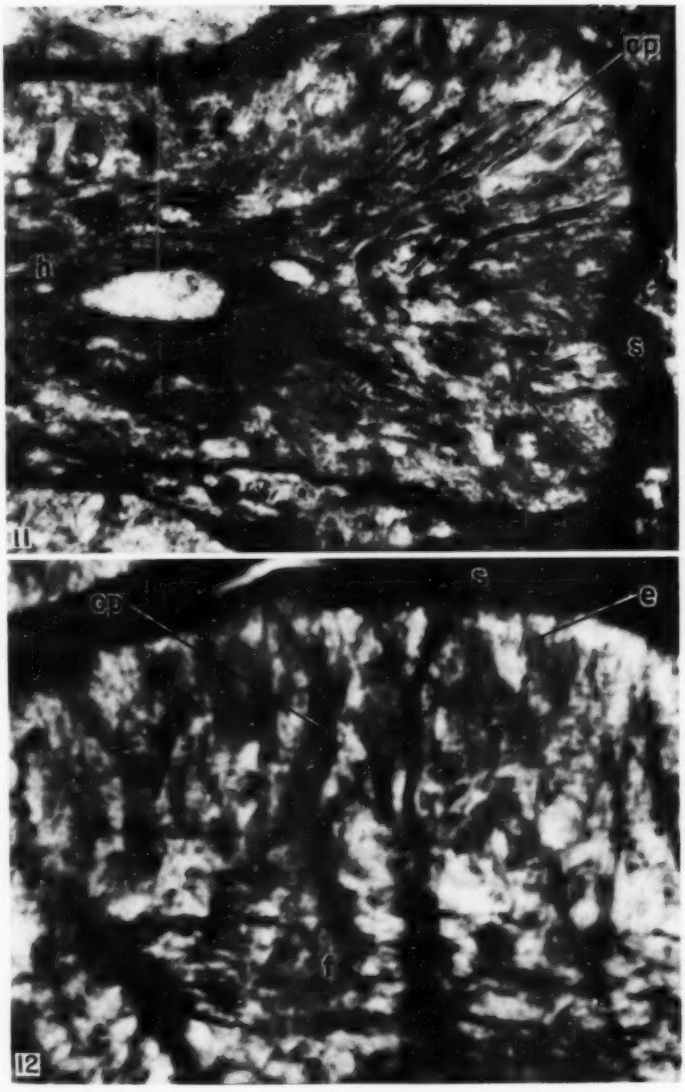


FIG. 11. Lobule of opossum neural lobe showing the cytoplasmic prolongations (cp) of the pituicyte fibers, which extend toward the septal layer (s) from the cell bodies in the hilum (h). Mallory-azan. ×660.

FIG. 12. Palisade layer of lobule of opossum neural lobe, with differential staining of both nerve fiber endings (e), and cytoplasmic prolongations of pituicytes (cp). f—nerve fibers in hilum. s—septal layer. Protargol. ×1800.

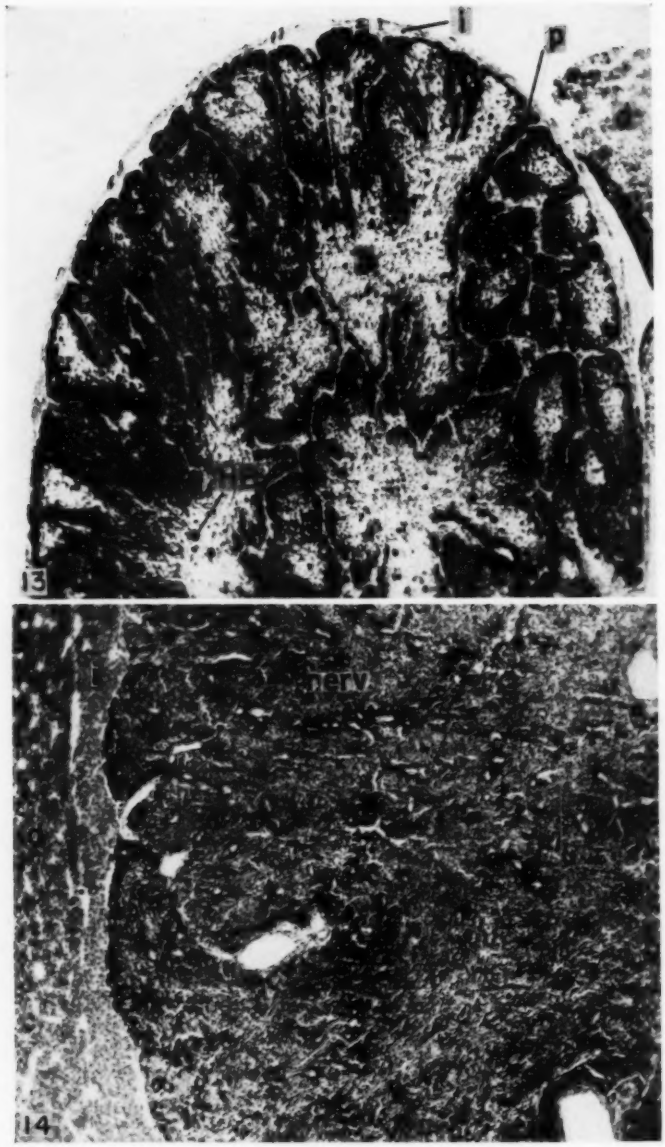


FIG. 13. Low power view of opossum neural lobe, stained with Gomori's hematoxylin method. The lobules are outlined by the dense staining of the palisade zone (p) surrounding the pale hilum (h) of each lobule. d—pars distalis. i—pars intermedia. HB—Herring body. ×75.

FIG. 14. Neural lobe (nerv.) of rhesus monkey, same stain and magnification. Lobulation very obscure, and neurosecretory substance less well localized than in opossum. d—pars distalis. i—pars intermedia. ×75.

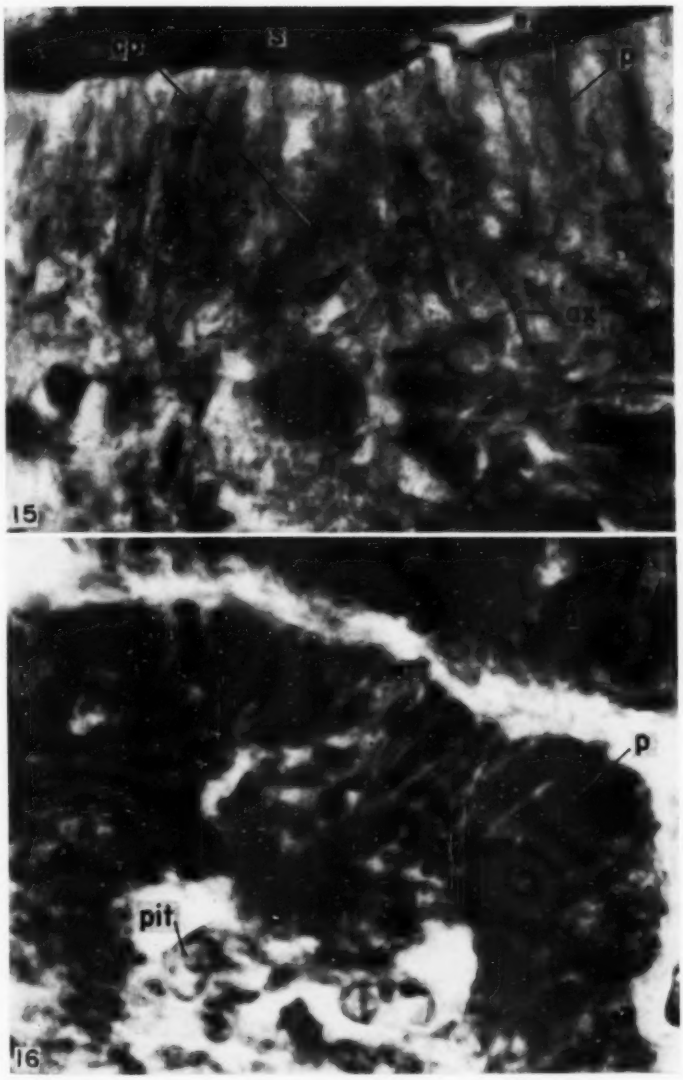
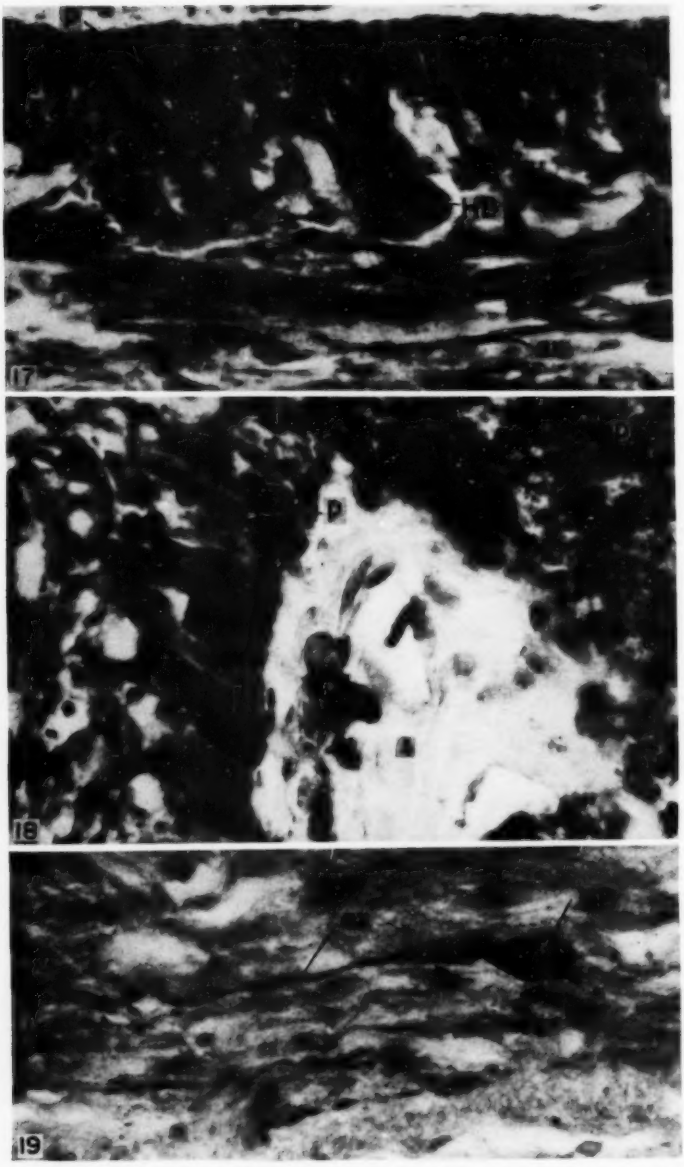


FIG. 15. Palisade zone (p) of neural lobe of opossum, with differential staining of nerve fiber endings (e) and cytoplasmic processes of pituicytes (cp). Note the palisade arrangement of the many axon terminals which end abruptly at the septal zone (s). ax—axon of hilum entering the palisade zone before breaking up into terminal arborizations. Protargol. ×1800.

FIG. 16. Palisade zone (p) of neural lobe of opossum, stained with Gomori hematoxylin method. The parallel rods perpendicular to the lobular margin appear to be composed of neurosecretory substance which encloses the nerve fiber endings. pit—nucleus of pituicyte in hilum of lobule. ×1900.



FIGS. 17, 18. Palisade zone (p) of opossum, stained with Gomori hematoxylin method, showing arrangement of rod-like nerve terminals, enclosed with neurosecretory substance. This animal had received the anti-diuretic drug, 3-hydroxy-2 phenylcinchoninic acid, and shows beginning depletion of neurosecretory substance in some of the terminal rods. ax—axon in hilum, well stained with the Gomori method, presumably because coated with neurosecretory substance. HB—Herring body at border between hilum and palisade zone. s—septal zone. At upper right in figure 18 are shown tangential sections of the terminal rods. ×900.

FIG. 19. Stalk of opossum neural lobe, showing axon (ax) terminating as a "Herring body" (HB). Both are well stained with the hematoxylin of the Gomori method. ×900.

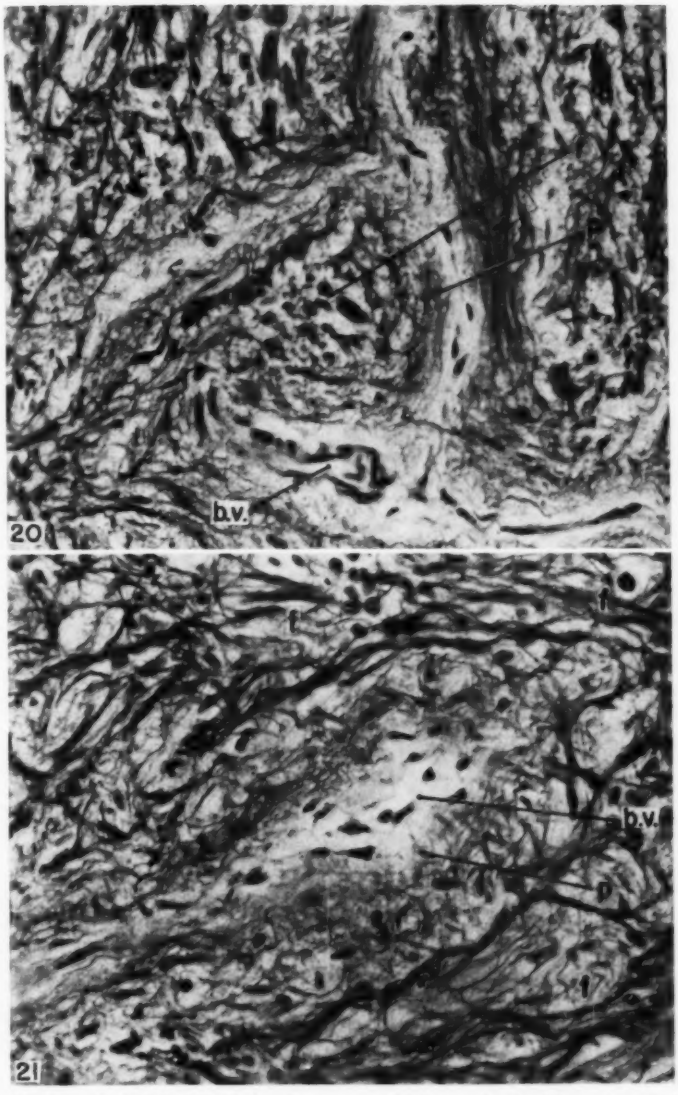


FIG. 20. A typical "lobule" of the rhesus neural lobe, stained with protargol. Compare with figure 7. The central hilum containing the nerve fibers of the hypophysial tract (f) is surrounded by a palisade zone (p) in which nerve terminal arborizations occur. The lobule is surrounded by connective tissue containing the blood vessels (b.v.). ×350.

FIG. 21. An "inverted lobule" of the rhesus neural lobe, with a central vessel (b.v.), surrounded in turn by the palisade zone (p) and the coarser nerve fibers derived from the hypophysial tract (f). ×350.

physial tract (Tello, 1912; Bucy, 1930). These terminal bulbs are present not only in the stalk (Figure 19), in the hilum of the gland (Figure 13), and of each lobule (Figure 8), but may also be seen in the recessus infundibuli as free bulbous endings of nerve fibers which extend through the epithelium (Figures 23–26). This curious termination of nerve fibers in the ventricular space, and

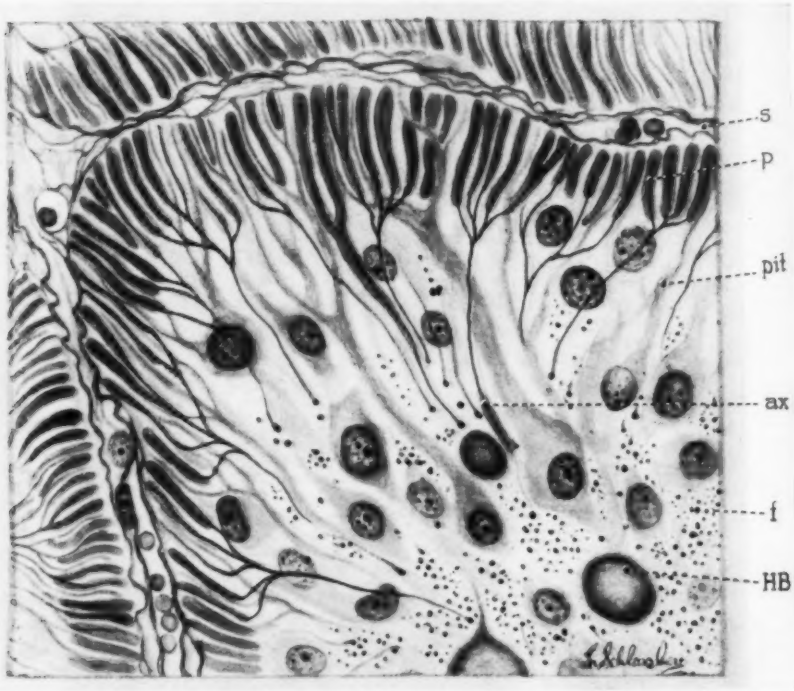
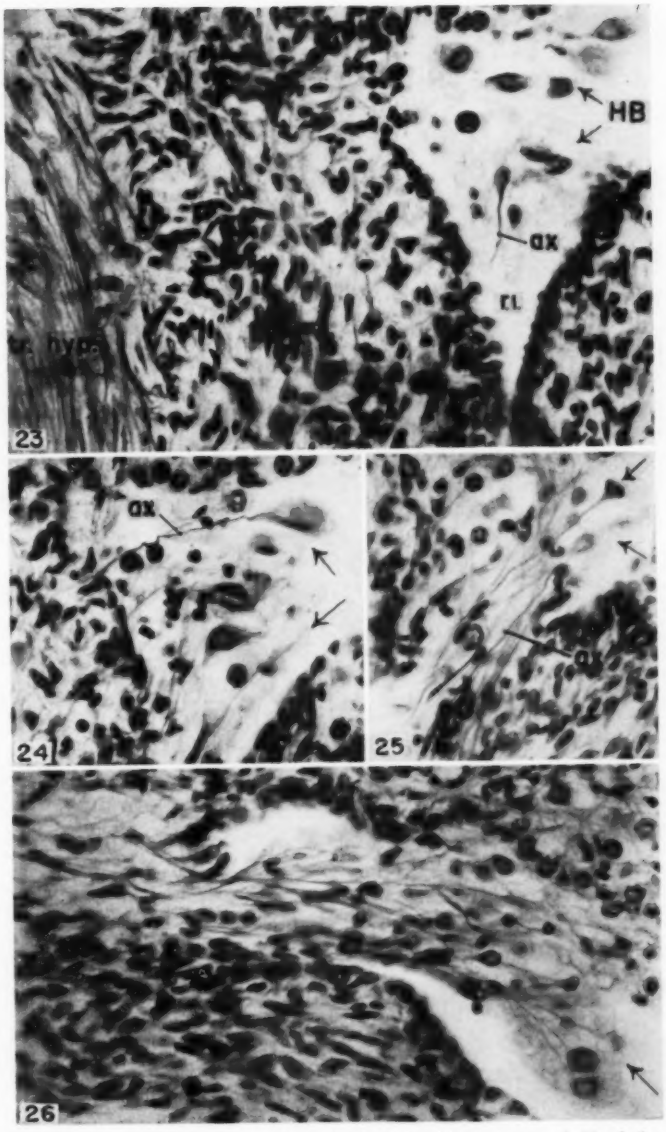


FIG. 22. Schematic representation of the histological organization of a neural lobe lobule, as seen in the opossum. Nerve fibers of the hypophysial tract (f), pituicyte cell bodies, and three Herring bodies (HB) are shown in the hilum of the lobule (lower right). Surrounding this, the palisade zone (p) is seen to be formed by nerve fiber terminals coated with a rod-like formation of neurosecretory substance. Interspersed are pituicyte fibers (pit) which extend to the vascular-collagenous septal layer (s). ax—axon about to form endings coated with neurosecretory substance.

the irregularity of occurrence of distribution of the Herring bodies in the gland proper suggests that these structures are terminal malformations of some nerve fibers (Tello, 1912). Their number and total mass would appear to be negligible as compared with the innumerable characteristic terminals described above. Like the typical rod-like terminals, the Herring bodies are also apparently coated with the Gomori-staining, neurosecretory substance, since when



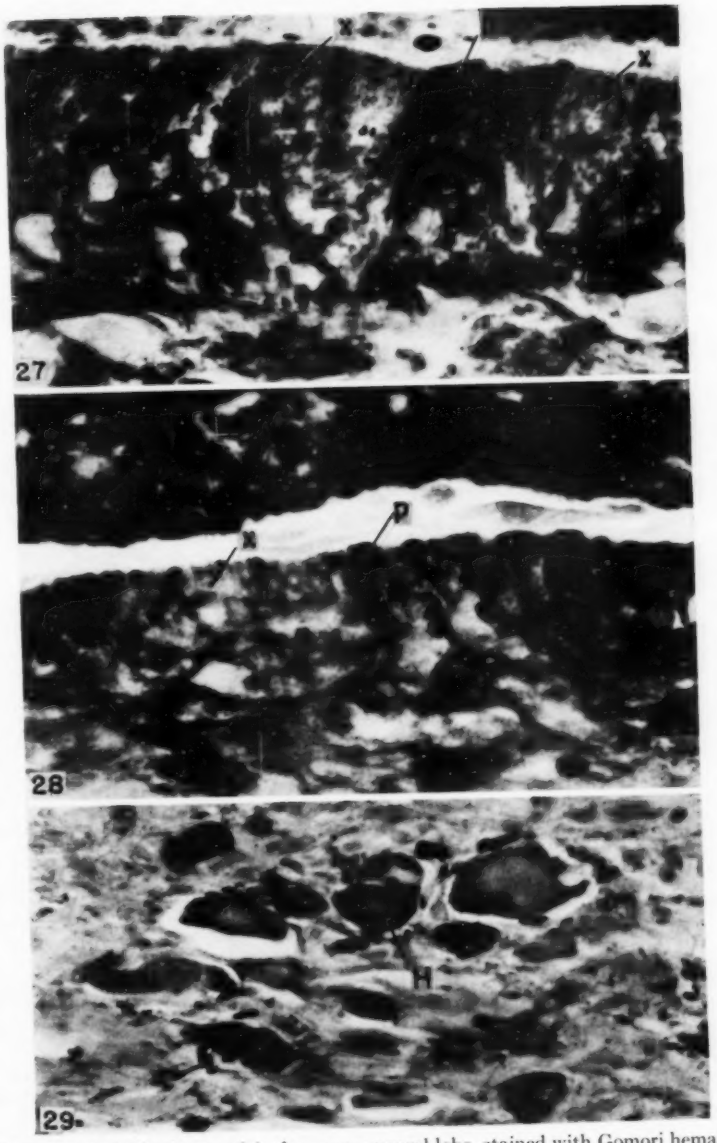
FIGS. 23–26. Consecutive sections through the infundibular recess (r.i.) of the opossum, showing nerve fibers (ax) penetrating the epithelium to terminate as Herring bodies (HB and arrows) in the ventricular space. tr. hyp.—hypophysial tract. ×350.

seen in optical section it is clear that the hematoxylin staining material is only present at or near the surface, whereas the core of the Herring body, or axoplasmic material, is stained pink by the phloxin of the Gomori mixture.

Significance of the Herring substance: Experiments with the antidiuretic drug, 3-hydroxy - 2 phenylcinchoninic acid. The presence of the Gomori-staining material (neurosecretory substance) in the entire hypothalamo-hypophysial system, all parts of which have been shown to contain adiuretin, vasopressin, and oxytocin (Hild and Zetter, 1951) is strong presumptive evidence for the concept that this substance is either the active principle of the neurohypophysial system or a precursor. More direct evidence has been offered by Ortmann (1951), who has reported that depletion of this substance occurs in the pars nervosa in animals deprived of water, and that apparent storage occurs when water intake was increased above normal. Salt administration added to water deprivation increased the depletion effect. Because of studies by Marshall and his colleagues (1949, 1950) showing that substituted cinchoninic acids are highly antidiuretic, that this effect is independent of changes in glomerular filtration, and that the hypothalamo-hypophysial system is concerned with the antidiuretic action of these drugs (Maren and Bodian, 1951), it was decided to test one of these drugs in the opossum, namely the 3-hydroxy - 2 phenylcinchoninic acid compound, generously supplied by the Department of Pharmacology at the Johns Hopkins University.

In a preliminary experiment, 2 adult opossums were given 50 mgms. per kilogram twice a day for 4 days, and 2 were given 150 mgms. according to the same schedule. Two additional animals served as controls throughout the experiment. The drug was administered subcutaneously as the sodium salt in aqueous solution containing 50 mgms. per ml. At the end of the fourth day all animals were perfused with Maximow's fluid, and prepared for histological study as described under MATERIAL AND METHODS.

In Gomori-stained preparations of the neurohypophysis or hypothalamus of animals given the small dose of drug, the only effect observed was a suggestion of depletion of the neurosecretory substance of some of the terminal rods in the palisade zone (Figures 17, 18). In animals receiving the larger dose, however, striking evidence of depletion of the neurosecretory substance was observed in Gomori-stained preparations of the pars nervosa (Figures 27–31). This depletion primarily involved the palisade zone (Figures 27, 28), but was also manifested to some extent in reduced stainability of some of the Herring bodies (Figure 29). In one of the animals the depletion of neurosecretory substance was accompanied by evidence of disorganization of the pattern of deposition of Gomori-staining material around the nerve endings, so that the lobular organization in such material was obscured (Figures 30, 31). Depletion of neurosecretory substance associated with cell bodies of the hypothalamo-hypophysial system was less apparent, but normally the intensity of stain is



FIGS. 27, 28. Palisade zone (p) of opossum neural lobe, stained with Gomori hematoxylin method and showing areas (x) of severe depletion of neurosecretory substance, following administration of the anti-diuretic drug, 3-hydroxy-2 phenylcinchoninic acid. ×900.

FIG. 29. Hilum of neural lobe, same section as shown in fig. 28. Some Herring bodies are intensely stained as in normal animals (H), while others appear to show depletion of neurosecretory substance in their peripheries. ×450.

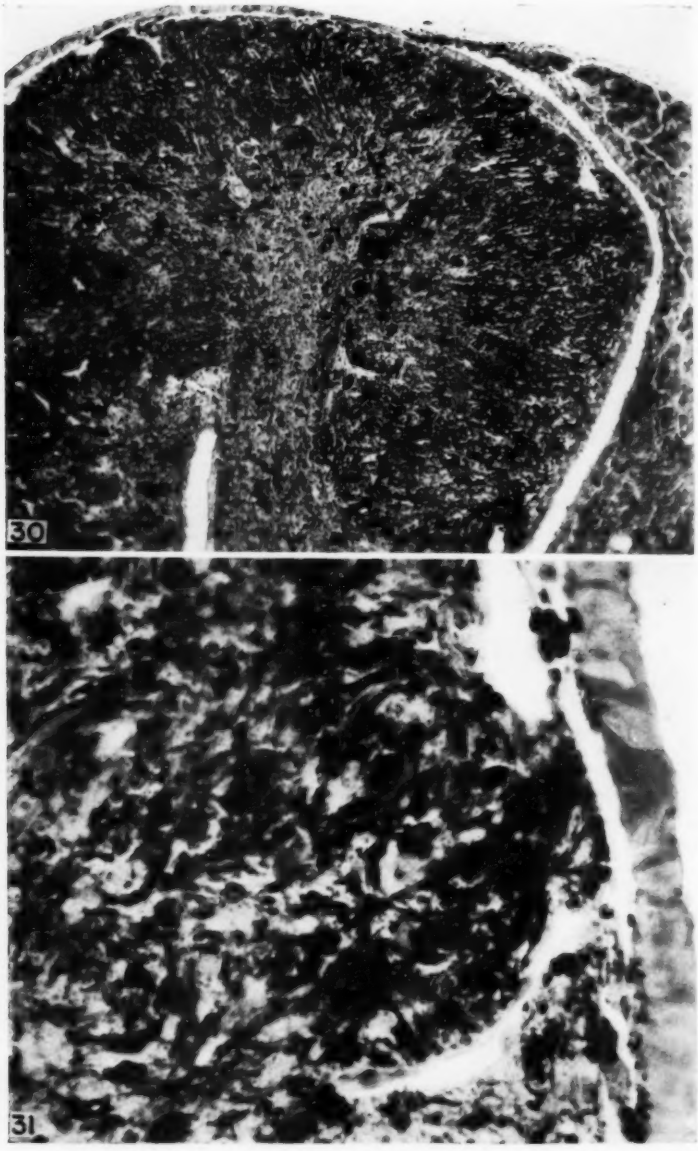


FIG. 30. Neural lobe of opossum stained with Gomori hematoxylin stain after 4 days of treatment with 3-hydroxy-2 phenylcinchoninic acid. Note that most of the Herring bodies in the gland are well stained, but that the lobules are obscured by the depletion of neurosecretory substance in the palisade zones. Lobular markings are also obscured by disorganization of nerve fiber terminals. Compare with fig. 13, showing normal gland. ×75.

FIG. 31. Same section as in fig. 30, showing disorganization of lobular architecture in a lobule containing more stainable neurosecretory substance than elsewhere in the section. Note collecting vein adjacent to pars intermedia on the right. ×460.

much less in these elements than in the pars nervosa, so that a detailed quantitative analysis would be necessary to establish the depletion in the cell bodies.

It would seem that the action of the substituted cinchoninic acids occurs by means of release of neurosecretory substance in the hypothalamo-hypophysial system, and in the opossum primarily in the pars nervosa. As in Ortmann's findings (1951), the antidiuretic hormone would therefore appear to be associated with the neurosecretory substance.

DISCUSSION

The structural details revealed by the opossum pars nervosa are of considerable interest to both the endocrinologist and the neurologist. It is clear that in this apparently primitive form of pars nervosa, the organ appears to be adapted to bring the nerve fiber terminal arborizations into relationship with the vessels of the septal layer. The pituicytes, which both separate and envelope the nerve fibers, appear to be adapted for contributing in some way to this relationship, rather than as primary glandular elements, innervated by the nerve fiber plexus. Because of the clear-cut aggregation of the neurosecretory substance in the opossum pars nervosa this species appears to be particularly favorable for histophysiological investigations of the functions of the neurohypophysis.

The presence of this material in association with the entire neuronal pathway of the hypothalamo-hypophysial system, as described and reviewed by Bargmann and Scharrer (1951) and Ortmann (1950) in other mammals, is confirmed in the opossum, with the added unsuspected finding that the innumerable terminal nerve fiber arborizations of this system are particularly associated with the neurosecretory substance. It is this finding which appears to give histological meaning to a gland which consists of a dense mass of nerve fibers, and associated neuroglia cells. The richness of the so-called innervation of the gland is far greater than can be imagined for any other function, including the presumed innervation of the pituicytes, often thought to be the secretory cells of the pars nervosa. In fact, in the opossum, the hypothalamo-hypophysial tract is seen to innervate no particular structure in the ordinary sense. Rather, the entire hypothalamo-hypophysial system, and especially the rich arborization of the nerve endings, is seemingly adapted to some unusual function. Rasmussen (1938) has stated the problem clearly as it applies to the human hypophysis. "There are at least 50,000 fine unmyelinated fibers descending from the hypothalamus into the infundibulum, and there are that many cells in one supraoptic nucleus. This relatively enormous nerve supply appears to be all out of proportion to the cellular content of the neural lobe, and to the amount of epithelium in pars tuberalis, pars infundibularis and pars intermedia."

Two principal hypotheses have been entertained regarding the site of origin of the neurosecretory substance. According to the idea proposed by Scharrer, and subsequently by others, the "neurosecretory granules" or neurosecretory substance are secreted in the cell bodies of the nerve cells of the hypothalamo-hypophysial system, and are transported along axons to the pars nervosa (Scharrer, 1936; Scharrer and Scharrer, 1945; Palay, 1945; Bargmann, 1949; Ortmann, 1951; Hild and Zetter, 1951). Although these workers have marshalled suggestive evidence for this point of view, it cannot be said that it has been conclusively proved. According to this concept, the much higher content of hormones in the pars nervosa as compared with the hypothalamic nuclei (Hild and Zetter, 1951) and the rich elaboration of nerve terminals in the pars nervosa would have to be conceived of as representing a morphologically complex storage system. An alternative hypothesis, mentioned but discarded by Palay (1945), is that the entire hypothalamo-hypophysial pathway may be concerned in the secretory process. Our findings regarding the rich terminal axon arborizations in the pars nervosa, and their close association with the neurosecretory substance, tends to support this concept, however. From this point of view, the morphological complexity of the nerve terminals becomes more readily rationalized as a mechanism for serving to increase the ratio of cell surface to cell volume, and perhaps thus favoring an enhancement of the secretory process in the pars nervosa, as compared with the hypothalamic nuclei. The best evidence thus far presented for the origin of the neurosecretory substance in the cell bodies is the reported finding of Ortmann (1951) that restitution of the Gomori-staining material after depletion occurs first in the cell bodies. This finding is important enough to require confirmation by quantitative studies of both the stainable substance and the active principle of the system. Moreover, the possibility that the nerve endings have been injured in these experiments, as suggested by Ortmann's finding of mitosis of pituicytes, must be considered. Such an effect might slow down the recovery of the secretory process in the nerve terminals as compared with the cell bodies. In our own experiments mitosis was not observed, possibly because of the short interval between onset of drug administration and death of animals.

In this connection it is interesting to note that the pressor and oxytocic action of extracts of the pars nervosa are similar to the actions of the adrenergic and cholinergic substances associated with synaptic loci in the peripheral and central nervous system. Moreover, the morphologic relationships of nerve endings in the pars nervosa support the view that nerve endings in general may be differentiated to secrete active substances, as well as to transmit electrical signals. The great specialization of nerve endings in the brain, for example (Bodian, 1942), both in form and in cytoplasmic constituents, suggest that some of them at least may be secreting active substances. These may not necessarily be transmitters, but may affect excitability thresholds of cells of termination.

Here is a problem which would seem to require the combined approaches of histology, chemistry, and electrophysiology, if we are to obtain a fuller understanding of why nerve endings are so greatly variable in appearance, and of how they really work.

SUMMARY

The opossum pars nervosa consists of lobules, outlined by vascular connective tissue septa, and constructed around branches of the hypothalamo-hypophysial tract. The tract is the hilum of the gland, and its branches, intermingled with Herring bodies and with the nucleated portions of pituicytes, form the hilum of each lobule. Between hilum and septal border of each lobule is a zone poor in nuclei. This zone can be best analysed in well-fixed material stained with silver or with Gomori's chrom-alum hematoxylin method which Bargmann has shown to reveal the specific material of the hypothalamo-hypophysial system (neurosecretory substance). Preparations treated with protargol reveal innumerable, fine, rod-like endings of nerve fibers of the hilum, arranged perpendicular to the septal border of the lobule. The hematoxylin of the Gomori stain selectively stains this zone, as well as Herring bodies in the hilum, and reveals the palisade arrangement of the neurosecretory substance, which appears to surround the nerve fiber terminals in sleeve-like fashion. Interspersed with these elements are pituicyte fibers which extend toward the septa like typical supporting glia cells. The morphologic relation of the nerve fiber terminals in the palisade zone, with their dense envelopment of neurosecretory substance, appears to be adapted to bring these elements into relationship with the blood vessels of the septal layer. Its clear-cut plan of organization makes the opossum pars nervosa admirably suited for histophysiological and histochemical studies. Preliminary studies with large doses of the antidiuretic compound, 3-hydroxy - 2 phenylcinchoninic acid show severe depletion of the neurosecretory substance in the pars nervosa, especially in the region of nerve endings, and some disorganization of the terminal nerve fiber pattern.

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CHANGES IN BLOOD VOLUME FOLLOWING OPERATION FOR PULMONIC STENOSIS: STUDIES WITH EVANS BLUE AND RADIOACTIVE PHOSPHORUS

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Received for publication August 3, 1951

We have recently made a study of blood volume in 20 patients with congenital cyanotic heart disease of the type associated with pulmonic stenosis and right to left intracardiac shunts (1). By combining the Evans Blue dye and radioactive phosphorus methods it was possible to make simultaneous direct measurements of plasma volume and whole blood volume. Cyanotic patients in both childhood and adult groups were found to have diminished plasma volume, greatly increased red cell volume and elevated whole blood volume when compared with non-cyanotic individuals.

Most of the patients whose studies comprised the previous report have been subsequently submitted to operation with the establishment of an anastomosis between a systemic and a pulmonary artery by the Blalock method (2) or by the Potts technique (3). It has been possible to carry out direct measurements of plasma volume and whole blood volume in 10 of these patients at periods of time varying from three and one half months to 13 months after operation.

METHOD AND PROCEDURE

The procedure followed is identical with that described in detail in the previous report (1). Twenty ml. of blood are drawn from a peripheral vein and incubated with approximately 50 microcuries of radioactive phosphorus for two hours at 37°C. The activated blood is then centrifuged, the plasma is removed, the red cells are washed in isotonic saline twice and then resuspended in saline. A 10 ml. aliquot of the radioactive cell saline suspension is then injected into a brachial vein along with 2 to 3 ml. of Evans Blue dye by means of a gravity infusion system. After a 15 minute mixing period a single 20 ml. blood sample is drawn from a vein in the opposite arm.

A 5 ml. aliquot of the radioactive cell saline suspension and of this blood specimen is centrifuged for one hour at 3200 RPM, the supernatant fluid is removed and the cells are hemolyzed by the addition of a saponin-sodium carbonate solution up to the original volume. Each of the specimens is diluted appropriately and then multiple 1 ml. portions are air dried overnight in ointment boxes in which a filter paper mat has previously been cemented. After further drying at 50°C, the radioactivity is measured with a Geiger-Muller tube and scaler.

$$\text{Whole Blood Volume } (WBV_{p32}) = \frac{A_1}{A_2} \times V$$

where: A_1 is the measured activity in counts/sec./ml. of the injected cell-saline suspension.

V is the volume in ml. of the injected cell-saline suspension.

A_2 is the measured activity in counts/sec./ml. of the 15 minute blood sample.

The color intensity of Evans Blue dye in a suitable dilution of plasma obtained from the 15 minute blood specimen is measured by means of an Evelyn photoelectric colorimeter equipped with Filter 620. Dye-free plasma obtained immediately prior to the infusion of the cell-saline suspension and dye serves after appropriate dilution as a plasma blank and in the determination of a dye calibration constant.

$$\text{Plasma Volume } (PV_{T1824}) = \frac{M \times K}{L_{620} \times d}$$

where: M is the milligrams of dye injected.

K is a calibration constant relating color intensity to dye content.

L_{620} is the average value of (2-log of galvanometer reading employing Filter 620) corrected for any hemolysis present.

d is the number of times the plasma is diluted before reading.

Red cell volume is presented as the difference between the directly determined whole blood volume and the directly determined plasma volume.

$$RCV = WBV_{p32} - PV_{T1824}$$

This quantity is divided by the directly determined whole blood volume to determine the "body" hematocrit of each patient.

$$\text{"Body" Hematocrit} = \frac{RCV}{WBV_{p32}} \times 100$$

RESULTS

Table 1 shows a summary of the observations in 10 patients with congenital cyanotic heart disease of the types associated with pulmonic stenosis and a right to left intracardiac shunt before and after operation to produce an artificial ductus arteriosus. The group consists of 4 female children and 3 female and 3 male adults. None of the patients showed any evidence of cardiac decompensation at the time the tests were done.

In each instance plasma volume represents the value determined directly by the dye method and whole blood volume is the value obtained by direct

measurement with the radiophosphorus procedure. Red cell volume is presented as the difference between these two directly determined values. This quantity in turn is divided by the directly determined whole blood volume to obtain the "body" hematocrit. Preoperative measurements were carried out shortly before operation in each instance, while postoperative studies were made at periods ranging from 3½ to 13 months after operation.

In 9 of the 10 patients the plasma volume has increased postoperatively by amounts ranging from 49 to 1394 ml. These 9 patients, each of whom was greatly improved by operation, showed a postoperative fall in peripheral

TABLE 1

Summary of Observations in 10 Patients with Pulmonic Stenosis before and after Operation

NO.*	SEX	STATUS	AGE	WEIGHT	HEIGHT	SURFACE AREA	PERIPHERAL HEMATOCRIT	PV_{T1824}	RCV ($WBV_{P32}-PV_{T1824}$)	WBV_{P32}	"BODY" HEMATOCRIT	CLINICAL DIAGNOSIS POSTOPERATIVE CLINICAL RESULT
			yrs.	*kg.*	*cms.*	*M²*						
19	M	Preoperative	19	52.3	180.3	1.66	74.7	1893	2987	4880	61.3	Tetralogy of Fallot
		Postoperative		52.7	177.8	1.65	43.7	3287	1313	4600	28.6	Excellent (3½ months)
5	F	Preoperative	9	23.6	132.1	0.94	75.0	1158	1912	3070	62.3	Tetralogy of Fallot
		Postoperative		28.0	138.4	1.05	49.3	1575	440	2015	21.8	Excellent (4 months)
10	F	Preoperative	11	27.3	142.2	1.06	76.5	943	1627	2570	63.3	Tetralogy of Fallot
		Postoperative		28.9	145.4	1.10	46.5	1670	620	2290	27.1	Excellent (6 months)
1	F	Preoperative	10	24.6	139.7	1.01	72.3	966	1274	2240	56.9	Tetralogy of Fallot
		Postoperative		28.6	151.4	1.14	48.0	1500	840	2340	35.9	Excellent (12½ months)
15	F	Preoperative	16	66.0	168.3	1.73	73.5	1897	2338	4235	55.2	Single Ventricle
		Postoperative		65.0	170.2	1.74	54.3	2655	1228	3883	31.6	Excellent (12 months)
20	M	Preoperative	21	54.1	175.3	1.66	76.3	2025	4175	6200	67.4	Tricuspid Atresia
		Postoperative		55.5	174.0	1.66	56.0	2980	2340	5320	44.0	Excellent (5 months)
3	F	Preoperative	9	29.9	134.7	1.06	57.3	1073	787	1860	42.4	Tetralogy of Fallot
		Postoperative		32.3	134.7	1.09	51.7	1122	518	1640	31.6	Good (6 months)
18	M	Preoperative	27	53.6	172.7	1.62	84.3	2300	6500	8800	73.9	Single Ventricle
		Postoperative		56.0	172.7	1.65	67.0	2810	3070	5880	52.2	Good (4 months)
11	F	Preoperative	22	50.0	170.0	1.56	73.0	1615	2080	3695	56.4	Tricuspid Atresia
		Postoperative		52.4	171.5	1.61	57.3	2208	1537	3745	41.4	Good (4 months)
12	F	Preoperative	18	51.6	157.3	1.50	74.0	1890	3280	5170	63.4	Pseudotruncus Arteriosus
		Postoperative		54.5	158.7	1.54	73.5	1810	2407	4217	57.0	Fair (13 months)

* Patient numbers are identical with those previously employed (1).

hematocrit ranging from 5.6 to 31.0 per cent and a decrease in red cell volume ranging from 269 to 3430 ml.

In one patient, the only one of the group studied who was not greatly improved by operation, the plasma volume has fallen 80 ml. This patient's peripheral hematocrit fell less than 1 per cent but there was a reduction in whole blood volume of 953 ml. and a 873 ml. drop in red cell volume.

Whole blood volume has decreased by 220 to 2920 ml. in 8 of the 10 patients. In two patients (✱1 and ✱11) each of whom was greatly improved by operation, whole blood volume was slightly increased after operation.

In order to make an accurate evaluation of the changes in blood volume after operation it is necessary to allow for the alterations in body size and weight that have taken place in these patients after successful surgical treatment. All but one of the 10 patients in this study have gained weight since operation and 3 of the 4 children have increased in height. Table 2 presents a comparison of the preoperative and postoperative values for plasma volume, red cell volume and whole blood volume in the 10 patients with body weight as a standard of reference. From this table it is seen that there is a decrease in red cell volume in each patient following operation ranging from 10.3 to 66.3 ml. per kilogram and averaging 31.80 ml. per kilogram. The whole blood volume has fallen in all patients by amounts varying from 2.4 to 58.9 ml. per kilogram and averaging 20.70 ml. per kilogram. Eight of the ten patients show an increase in plasma volume by increments of 7.2 to 26.2 ml. per kilogram

TABLE 2

Changes in Plasma, Red Cell, and Whole Blood Volume after Operation for Pulmonic Stenosis with Body Weight as a Standard of Reference

PATIENT NUMBER	PLASMA VOLUME (ML./KG.)			RED CELL VOLUME (ML./KG.)			WHOLE BLOOD VOLUME (ML./KG.)		
	Preoperative	Postoperative	Change	Preoperative	Postoperative	Change	Preoperative	Postoperative	Change
19	36.2	62.4	+26.2	57.0	24.9	−32.1	93.2	87.3	−5.9
5	49.0	56.2	+7.2	81.1	15.7	−65.4	130.1	71.9	−58.2
10	34.5	57.8	+23.3	59.6	21.4	−38.2	94.1	79.2	−14.9
1	39.3	52.5	+13.2	51.8	29.4	−22.4	91.1	81.9	−9.2
15	28.7	40.8	+12.1	35.6	18.9	−16.7	64.3	59.7	−4.6
20	37.5	53.7	+16.2	77.1	42.2	−34.9	114.6	95.9	−18.7
3	35.9	34.8	−1.1	26.3	16.0	−10.3	62.2	50.8	−11.4
18	42.8	50.2	+7.4	121.2	54.9	−66.3	164.0	105.1	−58.9
11	32.3	42.2	+9.9	41.6	29.3	−12.3	73.9	71.5	−2.4
12	36.6	33.2	−3.4	63.5	44.1	−19.4	100.1	77.3	−22.8

and averaging 14.44 ml. per kilogram. In two patients a slight reduction in plasma volume expressed on a weight basis has occurred following operation.

COMMENT

The changes in plasma, red cell and whole blood volume which occurred after the creation of a systemic-pulmonary anastomosis in this group of patients with pulmonic stenosis are illustrated in graphic fashion in Figure 1. In this figure the average values for the cyanotic patients before and after operation are compared with data from a group of normal adults compiled in a previous study (1).

After systemic-pulmonary anastomosis the subnormal plasma volume of the cyanotic patient rises to a level slightly higher than the normal, while the greatly elevated red cell volume is reduced to a value which, although less than half of its preoperative level, is still somewhat above the normal average.

Despite the 21 per cent reduction in whole blood volume after operation, this level in the postoperative patient with pulmonic stenosis remains approximately 15 per cent higher than the average normal value. The trend of these alterations is reflected by the peripheral hematocrit. The latter is greatly reduced after operation but nevertheless remains moderately elevated. The absolute change in the peripheral hematocrit is approximately paralleled by the change in the "body" hematocrit.

The patients in this study represent a random selection of cyanotic individuals with pulmonic stenosis and right to left intracardiac shunts. Diag-

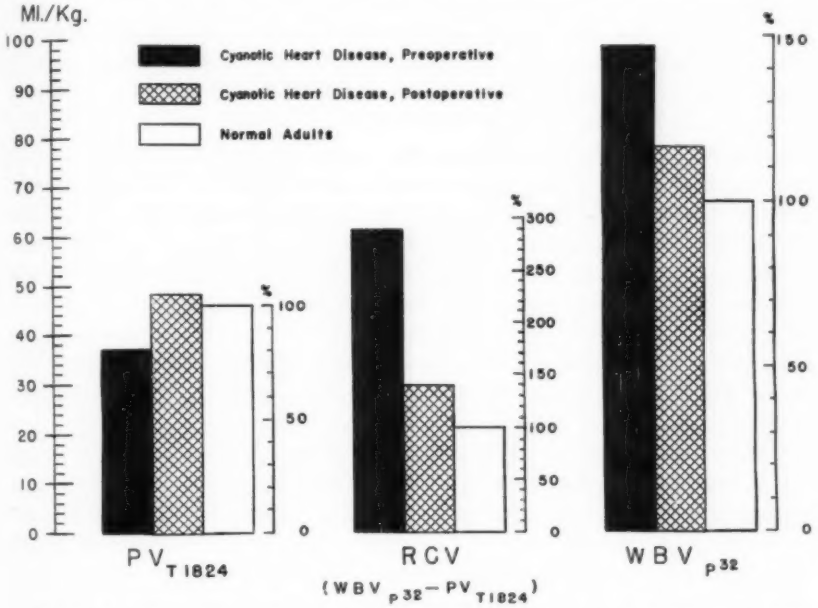

FIG. 1. Graphic comparison of average directly determined volumes of cyanotic patients before and after operation with normal averages.

noses include 5 patients with tetralogy of Fallot, 2 with tricuspid atresia, 2 with single ventricle, and one with pseudotruncus arteriosus. Operation resulted in functioning systemic-pulmonary anastomoses in each instance and as seen in Table 1 the clinical result of operation is satisfactory in all but one case. In this patient who has situs inversus, levocardia and pseudotruncus arteriosus an end to end anastomosis was done between the right subclavian and the right pulmonary artery. Cyanosis and polycythemia persist although the patient shows considerable improvement in exercise tolerance. Both clinical and laboratory evidence suggest that the effective pulmonary blood flow is still inadequate. The postoperative measurements of blood volume in this

instance fail to show a rise in plasma volume and the "body" hematocrit remains high (57.0). In the 9 other patients the clinical results of operation are quite satisfactory and the increase in pulmonary blood flow afforded by operation seems to be adequate. There is good correlation between the degree of general functional improvement in these patients and the magnitude of the changes in plasma and red cell volume. In general it appears that the best clinical results are associated with the greatest falls in "body" hematocrit.

Since only a single determination has been made on each patient of this study after operation, it is impossible to follow the progress of the alterations in the volume of the blood and its components with respect to time. Taussig (4) has reported a rapid fall in peripheral hematocrit in the first few weeks after successful operation with a subsequent slower approach toward normal levels. Josephs (5) studied the mechanism of reduction of red cells and hemoglobin in patients with tetralogy of Fallot after operation and found evidence for decreased red cell production as well as increased red cell destruction. His studies show that the latter, as measured by urobilin excretion, is greatly increased in the first week after operation. Employing only the Evans Blue dye method, Nelson, Mayerson, Clark and Lyons (6) made studies of blood volume in one patient with tetralogy of Fallot before and after a Blalock anastomosis. They found a marked reduction in red cell and whole blood volume 18 days after operation and repeated measurements on the 26th postoperative day showed even further diminution in these volumes. Studies carried out one month after this, however, showed no further decline in red cell or whole blood volume.

The available evidence, thus, indicates that the greatest reduction in red cell volume in cyanotic patients with pulmonic stenosis occurs in the first few weeks after operation. The present studies, carried out $3\frac{1}{2}$ to 13 months after operation in these patients, show that in addition to a great reduction in red cell volume, a rise in plasma volume has occurred with the result that whole blood volume, although somewhat reduced, remains moderately elevated. These studies suggest that the large postoperative decrease in red cell mass is compensated for in part by a rise in plasma volume and in part by a reduction in the size of the vascular bed. The failure of a complete return to "normal" levels in red cell volume in most of the patients following the operative establishment of adequate pulmonary blood flow is probably related to the persistence of a mild but definite degree of peripheral arterial oxygen unsaturation.

SUMMARY

Simultaneous direct measurements of plasma volume and whole blood volume using Evans Blue dye and radioactive phosphorus have been carried out in 10 patients with pulmonic stenosis immediately before and $3\frac{1}{2}$ to 13 months after operation. The results are presented in tabular form and are

compared with similar data from non-cyanotic subjects. After an adequate pulmonary blood flow has been established by operation there is in addition to a great reduction in red cell volume a rise in plasma volume with the result that whole blood volume although somewhat reduced remains moderately elevated.

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CEREBRAL LESIONS IN CONGENITAL HEART DISEASE

A Review of Autopsies on One Hundred and Sixty-Two Cases

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Received for publication August 15, 1951

Until very recent years, the complications occurring in patients having serious cardiac malformations have been studied almost entirely with academic interest, even though those complications have often been the immediate cause of the patient's death The prevailing attitude concerning the general problem of congenital heart disease has been expressed in a recent textbook: "Congenital malformations of the heart form a subject of great interest to the embryologist and pathologist. For the physician, in the present state of our knowledge, these conditions have far fewer attractions. Their physical signs are generally so obscure and equivocal, that a confident diagnosis of the lesions present is only occasionally possible during life; and even when it can be made, it is not often of any practical value" (1). Because of this quite understandable attitude, descriptions of the many pathological changes complicating congenital heart disease have often appeared more or less coincidentally in the reporting of cases or in the statistical surveys of larger numbers of these cardiac anomalies, although considerable interest has been afforded the development of bacterial endocarditis in these patients.

That cerebral lesions have a greatly increased frequency, often with fatal importance in patients with congenital heart disease, has long been recognized. As is customary in discussions of these conditions, a reference point may first be taken in Dr. Maude Abbott's classical presentation of 1000 cases of cardiac malformations where mention is made that 46 of these patients died from consequences of cerebral lesions (2). While discussions specifically concerned with observations of the cerebral complications of congenital heart disease have been scarce, doubtlessly due to the then academic aspect of the problem as well as to the improbability of any one physician or hospital to personally observe more than an occasional case of such anomalies, apparently this observation has been common knowledge and has appeared in textbooks, for example: "It is an old standing clinical observation that cases of congenital heart disease often suffered or died with signs of cerebral abscesses or emboli" (3). Taussig has repeatedly emphasized the importance of such lesions in her recent monograph on congenital cardiac malformations (4). In the past, Leech reported a series of 75 cases of cardiac malformations, in which mention was made of the 3 patients with massive cerebral infarction (5). Ford briefly discussed the occurrence of such lesions in patients with congenital heart disease (6). Terplan mentioned the occurrence of a massive cerebral infarction in a

review of 21 cases of serious cardiac deformities (7). Other authors described cases with such infarcts, particularly in discussions of the so-called *paradoxical* embolization.

Although no paper specifically concerned with cerebral infarction in congenital heart disease has been encountered, several recent reviews of the increased incidence of brain abscesses in such patients have appeared. Hanna reported 6 brain abscesses from a total of 160 cases of cardiac malformations (8). Robbins encountered 3 brain abscesses and Edwards 5 from 53 and 115 cases respectively (9, 10). Approximately 36 cases of brain abscesses in patients with congenital heart disease had been reported in the literature by 1948. In such reports, patients with a superimposed acute or subacute bacterial endocarditis, where cerebral as well as other embolic infections are so common, were usually not included. Again, in Abbott's summary 7 brain abscesses were listed.

Following the achievements of Gross and Hubbard (11), Crafoord and Nylin (12), and Blalock and Taussig (13), and the at least temporarily successful rehabilitation of large numbers of patients suffering from cyanotic or serious acyanotic heart disease, complications both of the cardiac anomaly and of the necessarily serious operative procedures became of great practical importance. Recent experience in the autopsy room as well as clinical observations have again indicated that cerebral lesions are among the most frequent of the serious complications. Bahnson and Ziegler, in a clinical review, reported that patients exhibiting signs and symptoms indicating serious cerebral disease apparently accounted for 22% of their postoperative deaths (14). Of these clinically diagnosed cerebral lesions, 50% were confirmed by autopsy, while many of the others did not come to post-mortem examination. It has thus seemed important to review the autopsy findings in cases of serious congenital heart disease with special regard to the occurrence of all types of cerebral lesions, and to determine, if possible, the pathogenesis of such lesions.

The study was made utilizing the records of autopsied cases in the Department of Pathology of The Johns Hopkins Hospital from January 1945 through December 1949. Naturally, only those cases where the examination included study of the cranial contents were considered. Routine paraffin sections stained by hematoxylin and eosin had been examined in all cases. Gross material had been studied by the prosector and had been reviewed by at least one and often by two experienced members of the Department of Pathology. All gross descriptions and final anatomical diagnoses were evaluated. Clinical histories on all cases were briefly abstracted.

Because of the great interest in patients with cardiac malformations at this Hospital during this period of time, coupled with the serious nature of the conditions and of the surgical procedure necessary for the improvement of that condition, relatively large numbers of autopsies on patients with cyanotic

heart disease had become available for study. Some of these cases, particularly those dying within the first month of life, showed the most bizarre cardiac malformations and it was decided to eliminate from this study all cases under one month of age as well as all with malformations which were so complicated as to make reasonable classification impossible. Only a rare example of the latter description was encountered in patients over one month of age. To enlarge the series for better statistical comparison with the group of patients with cyanotic heart disease, it was necessary to include in the group with acyanotic heart disease those patients coming to autopsy in this department during the past 15 years. Patency of the ductus arteriosis was not considered unless the patient was four months of age or unless the ductus had been clinically important as the cause of death at a somewhat younger age. Patencies of the foramen ovale or of the interatrial septum in the absence of other cardiac anomalies have not been studied. A total of 162 cases of congenital heart disease fulfilling these criteria have been studied, 135 of the cyanotic and 27 of the acyanotic type.

From Tables I through IV, it can be readily seen that both in operated and in non-operated cases cerebral lesions have occurred with considerable frequency in patients with all varieties of cyanotic heart disease. If the young age group of these patients is considered, it will at once be realized that this frequency is enormously higher than that in patients without cardiac malformations. A number of reasonable explanations for this greatly increased incidence of brain lesions are available and some of these will be discussed.

In the first place it seems clear that the majority of the recent or old infarcts seen in these cases have been produced by arterial or venous occlusion for most of the lesions were several centimeters to a size including a large portion of one hemisphere in extent and occasionally showed the distribution of a specific blood vessel. Focal necrosis of cerebral tissue may result from cerebral anoxia in the absence of vascular occlusions. Most workers, however, have found that the areas of necrosis developing in the brains of those experimental animals surviving severe anoxic episodes are quite small. The pathological changes in such experiments are usually found to be a diffuse or regional atrophy characterized by a loss of ganglion cells rather than by focal necroses, although the latter are also occasionally seen (15). Even repeated exposures to severe anoxia resulted only rarely in localized glial scars (16). In an autopsy report of a human surviving, after cardiac arrest for 10 minutes, for 26 days in an essentially "vegetable" state, diffuse loss of ganglion cells was seen without focal brain lesions (17). In our cases of congenital heart disease, 5 patients showed microscopic cerebral lesions which might well be considered compatible with recent focal anoxia necroses or with the glial scars resulting from old focal necroses due to diffuse anoxia alone. It should also be stated that small vascular occlusions doubtlessly would have resulted in similar anatomical

lesions and should be considered as the possible cause since, even though such vascular occlusions were not located in the sections studied, serial sections have not been made of such lesions. In addition, the cerebral tissues of other cases in Table IV contained perivascular petechial hemorrhages quite typical

TABLE I

Cerebral Lesions from 135 Cases of Congenital (Cyanotic) Heart Disease

Old Encephalomalacia

AGE HIST. NO. AUT. NO.	ANOMALY	LOCATION OF LESION	TYPE OF LESION	PATHOGENESIS	SYSTEMIC LESIONS	TIME OF DEATH POST-OPERATIVE	CLINICAL FEATURES
26 yrs. 511024 22006	Tetralogy of Fallot	Diffuse	Small old focal softening.	?	Organizing non-bacterial endocarditis.	1½ hrs.	Frequent headaches
9 yrs. 455375 21143	"	Right internal capsule and basal ganglia.	Old softening.	?	Fresh mural thrombus, left auricular appendage.	6 days	Left hemiplegia 10 mos. previously. Residual hemiplegia. Died in "heart failure".
3 yrs. 383680 19945		Right parietal lobe.	Massive old softening.	Thrombus in right middle cerebral artery.	Fresh fibrinous vegetations, I. V. septal defect and pul. valve. Recanalized thrombi pulmonary vessels.	No operation	Left hemiparesis after a syncopal attack. Died in syncopal attack.
16 yrs. 385672 19959	"	Diffuse	Old focal scars (microscopic)	?	Nodular scars on tricuspid and aortic valve.	10 hrs.	Hemiplegia at 6 yrs. Complete clinical recovery.
4 yrs. 406708 20315	Transposition of great vessels. Patent foramen ovale.	Left cortex and globus pallidum.	Large non-pigmented softening.	?	Focal scar, renal cortex. Recent duodenal ulcer.		History of two "strokes"
4 mos. A-71685	Pul. atresia. Patent foramen ovale. Patent ductus arteriosus.	Diffuse	Old focal scars (microscopic)	?	—	No operation	Negative

of recent severe diffuse anoxia. Six of the eight cases in this group died in the postoperative period so that the anoxia could be attributed to complications provoked by the surgical and anesthetic procedures. One patient, however, who was dead on arrival in the hospital, was also found to have these diffuse

TABLE II

Cerebral Lesions from 135 Cases of Congenital (Cyanotic) Heart Disease

Recent and Old Encephalomalacia

AGE HIST. NO. AUT. NO.	ANOMALY	LOCATION OF LESION	TYPE OF LESION	PATHOGENESIS	SYSTEMIC LESIONS	TIME OF DEATH POST-OPERATIVE	CLINICAL FEATURES
22 yrs. 425093 20642	Tetralogy of Fallot	Lenticulo-striate area and dentate nucleus.	Old softenings. Recent hemorrhagic infarct.	?	Old scar, myocardium. Recent renal infarct.	Died 8 days post operative in respiratory failure and shock.	Old hemiplegia with residual spasticity and blindness in rt. eye
4 yrs. 413253 20435	"	Diffuse	Multiple old microscopic scars. Recent massive hemorrhagic softening.	Thrombus in carotid artery?	Renal artery thrombosis. Recent renal infarct.	48 hours in coma with left sided weakness.	Fainting spells daily with occasional convulsion.
18 yrs. 401392 20262	"	Left int. cap. Frontal cortex.	Large old softening. Massive recent hemorrhagic infarct.	?	Yellow calcific masses on pulmonary valve. Recanalized thrombi in pulmonary vessels.	3 weeks	Convulsions post-operatively.
1½ yr. 407602 20324	Tricuspid atresia. Pulmonary atresia	Right cerebrum and left occipital lobe.	Old softening. Recent massive hemorrhagic softening.	?	—	30 hours	Unconscious at 1 yr. age for 1 hr. No residua. P.O. hemiplegia
14 mos. A-67948 21618	Trilocular heart with pulmonary atresia.	Right corpus striatum and left cerebral cortex.	Massive old softening. Recent hemorrhagic softening.	Right middle cerebral artery thrombus. Dural sinus thrombosis.	—	No operation	Hemiplegia at age of 6 mos.
5 yrs. 462951 21246	Transposition of great vessels. Tricuspid atresia.	Diffuse in cerebrum and cerebellum.	Diffuse focal softenings. Recent cerebellar infarct.	Surgical anastomosis left pulmonary artery to innominate vein.	Myocardial infarct. Recanalized thrombi in small pulmonary arteries.	2 days	Semicomatose post-operative.
3 yrs. 419970 20574	Transposition of great vessels.	Diffuse	Diffuse recent and old non-hemorrhagic softenings.	Meningeal arterial thromboses, recent and recanalizing.	Organized & recanalized thrombi in pulmonary vessels	20th day	C N.S. symptoms for 4 days prior to death
2 yrs. 503828 21862	Truncus arteriosus.	Frontal and parietal lobes	Old glial scars and recent hemorrhagic infarcts.	Thrombi in cerebral arteries.	—	15 hours	Not available.
4 yrs. 394522 20088	Tetralogy of Fallot.	Left cerebral cortex.	Massive old infarct, area of middle cerebral artery. Recent cortical hemorrhages.	?	Myocardial necroses. Organized and recanalized thrombi in pulmonary vessels.	24 hours	"Stroke", 9 mos. before death following unconscious attack. Residual hemiplegia.

TABLE III

Cerebral Lesions from 135 Cases of Cyanotic Congenital Heart Disease

Recent Infarction

AGE HIST. NO. AUT. NO.	ANOMALY	LOCATION OF LESION	TYPE OF LESION	PATHOGENESIS	SYSTEMIC LESIONS	TIME OF DEATH POST-OPERATIVE	CLINICAL FEATURES
2 yrs. 368812 19770	Tetralogy of Fallot	Right cerebral hemisphere.	Recent anemic infarction.	Thrombus in ligated carotid artery. Rt. middle cerebral artery thrombosis or embolization.	Pulmonary infarcts. Organized thrombi in small pulmonary vessels.	48 hours	Left hemiplegia on awakening from anesthesia.
16 yrs. (Syd) 20038	"	Right parietal lobe, temporal lobe, and pons.	Recent anemic and hemorrhagic infarcts, non-infected.	Acute bacterial endocarditis	Bland infarcts spleen and adrenal. Septic infarcts lung and kidneys.	No operation	Acute bacterial endocarditis, tricuspid, mitral and pulmonary valves.
17 yrs. 384373 20117	"	Right cerebral cortex.	Multiple recent and anemic and hemorrhagic infarcts.	Probable thrombosis rt. carotid artery above ligation.	—	6 days	Vertigo & transient blindness pre-operative. Hemiplegia post-operative.
4 yrs. 403409 20247	Tetralogy of Fallot with patent ductus arteriosus.	Diffuse	Multiple recent, anemic and hemorrhagic infarcts.	Cerebral arterial thromboses.	Thrombi in pulmonary vessels.	48 hours.	Post-operative convulsions.
3 yrs. 505457 21880	Tetralogy of Fallot	Diffuse	Multiple recent hemorrhagic cortical infarcts.	Thromboses cerebral veins.	—	24 hours	Frequent "spell" but never unconscious. Left facial weakness and rt. side flaccidity post-operative.
4 mos 520020 22092	Tetralogy of Fallot.	Both cerebral hemispheres.	Massive hemorrhagic infarcts.	Superior sagittal sinus thrombosis. (Probably ante-operation)	Old scar, kidney, ? old infarct. Organizing thrombi in small pulmonary arteries.	6 hours	Prolonged episodes of apnea, revived by artificial respiration.
5 mos. A-72375 22076	Mitral and pulmonary atresias.	Both cerebral hemispheres.	Massive hemorrhagic infarctions	Sinus thrombosis.	Pulmonary infarction. Thrombi in pulmonary vessels.	No operation.	Convulsions 2 weeks prior to death.
3 mos. A-67458 21580	Mitral atresia. Transposition of great vessels. Rudimentary outlet chamber.	Left frontal lobe.	Hemorrhagic infarct.	Thrombosis of meningeal veins.	—	1 day	Episodes of unconsciousness.

Table III—*Cont.*

AGE HIST. NO AUT. NO.	ANOMALY	LOCATION OF LESION	TYPE OF LESION	PATHOGENESIS	SYSTEMIC LESIONS	TIME OF DEATH POST-OPERATIVE	CLINICAL FEATURES
1 yr. A-61111 21118	Transposition of great vessels.	Rt. cerebral hemisphere	Massive hemorrhagic infarct.	?	Thrombi pulmonary arterioles	—	Died suddendenly preoperatively.
4 mos. A-60562 21082	"	Right temporal, rt. & left frontal lobes and corpus striatum.	Recent anemic infarcts.	Thrombus at site of pul. art.-vena cava anastomosis. Thrombi (?emboli) rt. carotid & middle cerebral arteries.	Pulmonary infarcts. Thrombi in pulmonary vessels.	3 days	Neg. preoperatively.

"anoxic" petechiae. It must be pointed out that our material has not been studied with regard to diffuse ganglion cell loss and such investigations are certainly indicated. In this respect it is of particular interest that a loss of intelligence has not been noticed even in those children with the most severe cyanosis and reduced oxygen saturation, although this feature too has not been studied by special efforts. In the present series of cases of congenital heart disease, a reasonable number of patients developed significant clinical signs and symptoms of central nervous system dysfunction often leading to the clinical diagnosis of: "cerebral infarction", or "cerebrovascular accident," etc., when the routine post-mortem examination could find no morphological alterations in the brain. Initial examinations by skilled neuropathologists using special techniques would have been expected to have shown among these cases incidences of cell changes in the affected cerebral areas.

If then we consider that the majority of the cerebral infarcts were produced by specific vascular occlusions, the polycythaemia so dramatically present in most of the patients with cyanotic heart disease must be recognized as a most important factor responsible for those occlusions whether the occlusions developed as an in situ thrombosis, or as cerebral emboli from thrombosis in other locations. There is no question that the degree of polycythaemia present in many of these patients resulted in a greatly increased blood viscosity. That the increased viscosity produced a sluggish blood flow has been well recognized and thrombosis of course is imminently related to the latter. It has been even suggested that increased blood viscosity in some manner produces vascular endothelial damage which of course would further predispose to local thrombosis. No direct evidence demonstrating this latter suggestion has been found but the possible role of such a phenomenon is of obvious importance and

should be investigated. In polycythaemia vera of adults, levels of 7 to 10 million red blood cells and 18 to 24 grams of hemoglobin are occasionally found, quite in the ranges often seen in patients with cyanotic heart disease. In such patients with polycythaemia vera, the occurrence of thromboses is notoriously common. The literature contains many references discussing the

TABLE IV

Cerebral Lesions from 135 Cases of Cyanotic Congenital Heart Disease

Recent Hemorrhage

AGE HIST. NO. AUT. NO.	ANOMALY	LOCATION OF LESION	TYPE OF LESION	PATHO-GENESIS	SYSTEMIC LESIONS	TIME OF DEATH POST-OP-ERATIVE	CLINICAL FEATURES
14 mos. A-70753 21836	Transposition of great vessels	Diffuse	Microscopic perivascular hemorrhages.	? anoxia	Organizing pulmonary art. thrombi.	—	Child dead on arrival
3 mos. 522896 22145	"	Subarachnoid	Multiple subarachnoid hemorrhages.	?	Organizing thrombi in pulmonary arteries.	Few hours	—
5½ yrs. A-44486 19697	Tetralogy of Fallot	Diffuse	Small hemorrhages and perivascular leucocytes, ? early infarct.	?	Thrombi in pulmonary arterioles	15 hours	Right side spasticity and left facial paralysis on admission.
5 yrs. 395099 20100	"	Diffuse in cerebral cortex and cerebellum	Small hemorrhages.	?	Hyaline ?vegetation, pulmonary conus. Recent and organized thrombi in pulmonary vessels.	18 hours	Post-op. convulsions.
2 yrs. 412684 20430	"	Cortical grey and white matter.	Small hemorrhages, up to 1 cm. size.	?	Organizing thrombi in pulmonary vessels.	12 hours	Post op. convulsions. Previous attacks fainting.
4 yrs. 422969 20599	"	Diffuse	Petechial hemorrhages.	? anoxia	Small thrombi coronary arteries.	12 hours	Died after massive hemorrhage.
6 yrs. 437323 20823	"	Internal capsule	Microscopic hemorrhages in internal capsule.	?	Thrombi in pulmonary artery.	14 hours	Pre-operative convulsion. Post-operative hemiplegia.
15 mos. A-71491 21909	"	Diffuse	Petechial hemorrhages.	?	—	3 days	Sudden cyanosis and death.

systemic infarcts, including infarctions of the brain, in these patients (18, 19). Neurological abnormalities primarily related to the cerebrum are also seen in patients with polycythaemia vera in the absence of more specific evidences of infarctions since headache, vertigo, visual disturbances and even loss of consciousness have been noted and psychoses, chorea, and hallucinations in these patients have also been mentioned. Some of the patients with such definite

cerebral symptomatology were not shown to have been recognizable cerebral lesions at autopsy, leading to the suggestions that cerebral anoxia had resulted in cell dysfunction without demonstrable cell damage. Complicating the comparison of polycythaemia vera with congenital cyanotic heart disease is the older age of the former group and its concomitant arteriosclerosis. It might be noted that polycythaemia vera in childhood is very uncommon but in several reports by Wieland of a family with what might be considered childhood polycythaemia vera, no descriptions of thrombotic lesions were given, although no autopsies had been performed (20). It has also been found that blood platelets and blood calcium levels have often been elevated in patients with polycythaemia vera. We have not been able to find any studies on the platelet or calcium levels in congenital heart disease and our cases did not contain such information.

It is unfortunate that it is difficult to compare the relative incidence of thrombotic lesions in cases of cyanotic heart disease with those in the acyanotic type of disease where polycythaemia is not present but where similar lesions were found. The small numbers of cases of the latter group studied in our series makes such a comparison unreliable. It does appear that the cerebral lesions found in the acyanotic group are of a different variety or, where related to thromboses, other obvious causes for the thrombosis or embolism such as heart failure or arteriosclerosis were present. Furthermore, when a comparison is made of the degree of polycythaemia present in the cases of cyanotic heart disease showing thrombotic lesions with the degree of polycythaemia present in those without lesions, no essential differences were found. This comparison was possible in 62 cases of tetralogy of Fallot. The 13 cases with cerebral infarction or thrombi showed no greater elevation of the polycythaemia insofar as the terminal hospital stay was concerned than did the 49 cases without lesions. Of course, transient elevations of polycythaemia, as with dehydration during recurrent illnesses or hot weather, may play an important role in initiating the thrombus formation. Taussig emphasizes the importance of preventing the occurrence of dehydration in these patients.

Recognizing the existence of marked polycythaemia in these patients, and its great predisposition to intravascular thrombosis, it seems altogether reasonable that any condition leading to additional polycythaemia, to vascular endothelial damage or to reduced blood flow locally or generalized, however slight or transitory, might well result in prompt intravascular thrombosis. Several factors resulting in such changes in these patients with congenital heart disease deserve consideration.

It may be seen from the tables that many of these patients suffered from attacks of fainting or unconsciousness sometimes associated with convulsions. These syncopal attacks lasted from a few seconds to hours. One of the patients gave the history of hemiplegia on awakening from one of many such

attacks. The alterations of cardiac output and cerebral blood flow during these episodes in these patients can only be speculated upon but the blood pressure fell during such an attack in at least one patient. Cyanosis becomes markedly accentuated in a majority of the attacks and it is quite possible that

TABLE V

Cerebral Lesions from 27 Cases of Acyanotic Congenital Heart Disease

All Lesions

AGE HIST. NO. AUT. NO.	ANOMALY	LOCATION OF LESION	TYPE OF LESION	PATHOGENESIS	SYSTEMIC LESIONS	TIME OF DEATH POST-OPERATIVE	CLINICAL FEATURES
2½ yrs. 329754 19238	Coarctation of aorta	Left parietal lobe	Old infarction	Recanalized thrombus, left middle cerebral artery.	—	—	History of heart failure and hemiplegia.
13 yrs. 44240 8 20925	"	Left cerebral hemisphere	Recent massive softening left anterior cerebrum.	Arteriosclerotic plaque left internal carotid artery with superimposed recent thrombus.	—	5 days	Hemiplegia on awakening from anesthesia
40 yrs. 161659 16345	"	Subarachnoid space.	Massive hemorrhage.	Congenital aneurysm of circle of Willis	—	—	—
49 yrs. 407081 21347	"	"	"	"	—	—	—
41 yrs. 514604 22035	"	"	"	"	—	Died during operation	—
58 yrs. U74197 16659	"	Circle of Willis	Multiple aneurysms of circle of Willis.	—	Calcific aortic stenosis	—	Sudden death.
26 yrs. 126456 21147	Patent ductus arteriosus	Subarachnoid space.	Subarachnoid hemorrhage	Congenital aneurysm of circle of Willis.	—	—	Died months after successful ligation of the patent ductus.
22 yrs. 165759 18542	Interventricular septal defect.	Occipital lobe.	Brain abscess	Acute osteomyelitis.	Liver abscess	—	Acute osteomyelitis for 2 months with headache for 1 week.

cardiac output and cerebral blood flow may be reduced. Vasodilatation occurring as a result of excessive tissue anoxia would certainly lead to a reduction in the rate of blood flow. It might also be pointed out that asphyxiation alone is known to result in an increase in circulating blood platelets, although the effect of such cyanotic attacks in these patients on blood platelets is not

known. However, all of these factors may function to predispose to intravascular thrombosis during these not infrequent episodes of sudden increased cyanosis, fainting or other central nervous system symptoms in patients with cyanotic heart disease.

An additional feature of great importance in this series is the severe surgical procedure necessary for the alleviation of the anomalous circulation. Of our 19 cases with recent cerebral infarctions, 15 were found in patients dying in the postoperative period which varied from 6 hours to 20 days. The occurrence, however brief, of dehydration, anoxia, or shock during or immediately after the operation doubtlessly results in a transient increased tendency to thrombus formation by way of the comcomitant rise in blood viscosity and depression in already sluggish blood flow. Circulating blood platelets have long been known to undergo marked increases, as much as 30 to 100% of their original values, as a result of significant operative procedures although the actual response in these cases is not known (21). Such platelet increases may be of additional importance to the factors already mentioned augmenting the already strong predisposition to intravascular thromboses. This group of surgical cases is particularly interesting in regard to the search for the usual source of the cerebral thrombi in all cases of cyanotic heart disease for it seems clear that while venous thrombi may commence formation during or immediately after any surgical procedure, these thrombi usually do not provide emboli for several days. Many of the postoperative patients however showed the evidence of cerebral damage on awakening from anesthesia and most of the infarctions occurring during or after surgical procedures were of the hemorrhagic variety, indicating that their origin was from venous vascular occlusions which must have arisen by in situ cerebral vein thrombosis. The surgical procedures, however, also provide a nidus for the formation of thrombi capable of embolizing or propagating into cerebral arteries. When the distal end of the ligated artery or vein which was anastomosed with the pulmonary artery or with other vessels remains in continuity with the vessels to the brain, thrombi forming in the blind end of the ligated vessel or at the actual site of anastomosis may well propagate cephalad to occlude cerebral blood flow. Such thrombi may also form the origin of emboli to the brain. Thrombotic lesions at the site of the vascular surgery, presenting at least the anatomical possibility of being the source of the cerebral emboli, were found in 3 of the 15 cases dying in the immediate postoperative period. One was a thrombus found at the site of anastomosis of the pulmonary artery and vena cava in a patient with thrombotic occlusion of the middle cerebral artery and with resulting cerebral infarctions. The other 2 showed thrombi in the carotid artery at and above the site of surgical ligation. While the surgical ligation of a carotid artery would not in itself result in cerebral infarcts of the variety seen in most of our cases, such a reduction in blood flow would further predispose to a

sluggish cerebral flow with its dangers of in situ thrombosis as well as reducing markedly the possible protection by collateral blood flow of cerebral tissues compromised by the developing venous or arterial thrombosis. The occlusion of the right carotid artery was not infrequently necessary when the innominate or the proximal portion of the right carotid itself was used for the surgical anastomosis.

The specific thrombus in a cerebral vessel responsible for the infarctions was not often found but the difficulties in locating such lesions in the brain are well recognized. Five of our cases were seen to have had thromboses of cerebral veins or of the dural sinuses and at least 9 other cases demonstrated hemorrhagic infarcts which indicated their probable origin from venous thromboses. It would naturally be expected that a sluggish blood flow would result in venous thrombosis far more frequently than in in situ arterial thrombosis. However, anemic infarcts were also common and some of these showed in a striking manner the distribution of a specific cerebral artery such as the middle cerebral or branch of the lenticulo-striate artery. Thrombi were actually found in a carotid artery 3 times, in the right middle cerebral artery 4 times and in smaller cerebral or meningeal arteries 3 times.

The origin for the possible cerebral emboli in most instances could not be definitely established. That the parent thrombi rarely may have developed in the vicinity of the surgical procedure has been mentioned. That thrombi developed in peripheral veins and reached the brain as so-called *paradoxical* emboli through cardiac defects is a definite possibility. Indeed, the literature assumes that the majority of systemic arterial thrombi found in patients with cardiac defects permitting the direct passage of venous blood into the systemic arterial bed resulted from paradoxical embolization even though no positive evidence was presented in the majority of reported cases. Evidences of peripheral venous thromboses such as leg edema or pain has been lacking in our cases. Venous thromboses in viscera have not been encountered frequently although these could have been easily overlooked. Furthermore, as an alternative source for emboli, the anomalous circulation in the cardiac chambers undoubtedly provides eddy currents in blood flow as well as isolated pockets of stasis, both ideal for the formation of intracardiac thrombi. We see further evidence for this possible source of cerebral emboli in the not infrequent appearance of nonbacterial vegetations on or adjacent to stenotic or malformed orifices. Six such lesions were found among the cases with cerebral lesions, and could be suggested as possible sources for thrombi to embolize either the systemic or pulmonary circulations. Cardiac failure, which may intervene during the clinical course of these patients with cardiac anomalies, has not proved a prominent feature from most of the clinical records. The development of thrombi, however, in cardiac chambers during its decompensation is a well recognized complication. Indeed, in some of the cases reported in the literature to have

shown paradoxical embolization, cardiac failure had been present, invalidating the necessity for assuming the paradoxical spread of emboli from the venous circulation. The failure to find cardiac thrombi at autopsy, whatever their pathogenesis may be, in no way eliminates the heart as the source for emboli since such thrombi are often not attached to the endocardium and their prior presence has been justly assumed from the frequent occurrence of systemic arterial emboli in decompensated patients in the absence of cardiac defects. It thus seems quite evident that there are several possible factors occurring within the cardiac chambers predisposing towards the formation of intracardiac thrombi capable of embolizing the peripheral circulation. In our series, 1 patient dying 6 days postoperatively with a tetralogy of Fallot in heart failure showed fresh mural thrombi in the left auricular appendage. No other cases with cardiac thrombi were seen other than those in association with fixed vegetations. It must be stated that after considering a number of possible sources for the development of thrombi so located as to form emboli to the brain, we are not able to establish any particular site as that usually occurring in these patients and it seems altogether reasonable that all of these mechanisms for cerebral emboli may be at times responsible in any large group of cases.

Systemic infarcts in organs other than the brain have also been common in this group of patients. Eight of the 25 patients with cerebral infarcts showed infarctions in either the lungs, heart, kidneys or spleen. This observation does not help in determining the source for the thromboses but lends emphasis to the problem of thromboembolism in patients with congenital heart disease. It may be of significance that of those 110 patients having no cerebral lesions, only 10 showed other systemic infarcts.

Pulmonary thrombi of the peculiar recanalizing variety described by Rich (22) were often found. Fourteen of the 23 patients with tetralogy of Fallot having cerebral lesions showed these small pulmonary vascular thrombi. Their pathogenesis, discussed by Rich, is no doubt closely related to the mechanism of production of the cerebral vascular lesions. It is noteworthy that of the 10 cases of transposition of the great vessels with cerebral lesions, all had pulmonary vascular thrombi in spite of what would be supposed to be a very adequate pulmonary blood flow. As might be expected, these thrombi, when recanalizing, did not show the peculiar cavernous-like structure seen in those patients with reduced pulmonary flow.

The occurrence of 5 cases of brain abscesses in our series of patients with cardiac malformations in general agrees with the incidence reported in the literature (8, 9, 10). While statistical analyses are impossible with such a small number of cases available, it seems quite reasonable to feel that brain abscesses occur with a much greater frequency in such patients than in the general populace. It is furthermore apparent that, if bacterial endocarditis superim-

posed on cardiac or vascular defects is eliminated, the abscesses occur for the most part in those cardiac malformations classified as cyanotic heart disease where the venous blood continually or intermittently passes directly into the peripheral arterial system. Four of our cases were found with these malformations, for the 1 patient with a so-called *pure* pulmonic stenosis had a patent foramen ovale. It should be emphasized, however, that 1 of our patients had

TABLE VI

Cerebral Lesions from 162 Cases of Congenital Heart Disease

Brain Abscess

AGE HIST. NO. AUT. No.	ANOMALY	LOCATION OF LESION	TYPE OF LESION	PATHOGENESIS	SYSTEMIC LESIONS	TIME OF DEATH POST-OPERATIVE	CLINICAL FEATURES
9 yrs. 425079 22120	Pulmonary stenosis.	Left frontal lobe.	Solitary abscess.	?	—	72 hours after valvulotomy. 20 hours after drainage of abscess.	Headaches 2 months. Ptosis and irrational 48 hours postoperatively.
22 yrs. 165759 18542	Interventricular septal defect.	Right occipital lobe.	Solitary abscess with old and recent activity.	Osteomyelitis, leg.	Liver abscess	—	Rapid onset of headache and death within week.
10 yrs. 419945 20557	Tetralogy of Fallot.	Left temporal lobe, frontal lobe and pons.	Multiple actinomycotic abscesses.	"Meningitis" 1 yr. prior to death.	—	60 hrs.	Residual right weakness after meningitis. Increasing rt. weakness and coma postoperatively.
5 yrs. 472022 21375	"	Left parietal lobe.	Solitary old abscess, with penetration of meninges and meningitis.	?	Thrombi in pulmonary arteries.	—	Fever, convulsions, and residual hemiparesis, June 1948. Death Sept. 1948.
6 yrs. 441145 21531	"	Right frontal	Solitary old abscess.	?	—	Shortly after operation	Febrile illness with hemiparesis. Surgical removal brain abscess.

a simple interventricular septal defect, a true *Maladie de Roger*, in which no cyanosis was present and where it may be reasonably assumed that the vascular shunt was entirely left to right. The usual hypotheses have been that these abscesses are the result of cerebral embolization through cardiac defects by infected venous thrombi or that the venous blood, thought to be occasionally carrying pathogenic organisms normally *filtered* out of the blood as it passes the pulmonary capillaries, directly enters the systemic circulation and in this manner carries the infection to the brain. In respect to this latter pos-

tulate, it may be of interest to point out that while it certainly has not been proven, experiments have indicated that it may be difficult to produce abscesses in cerebral tissues by the direct injection of bacteria without the production of cerebral damage either by prior trauma or trauma at the time of the bacterial injections (23, 24, 25). These experiments are not sufficiently conclusive to warrant the assumption that in patients with congenital heart disease, a focus of cerebral necrosis or infarction always preceded the development of the brain abscess. As others have also pointed out, the development of infection in an area of damaged cerebral tissue from transient and ordinarily innocuous bacteremia may be considered, however, a third possibility in the pathogenesis of such abscesses in these patients. In 1 case in the literature small abscesses were said to be located in a larger infarct (8). In our case with the interventricular septal defect, the source of the infection was surely the site of an active osteomyelitis which had been present in one leg. This patient also had a liver abscess. It would seem reasonable to consider that this patient developed a pyemia and the presence of the cardiac malformation did not necessarily play a role in the formation of the cerebral abscess. A case revealing multiple actinomycotic abscesses had "meningitis" a year previously from which he had never fully recovered. The 3 other cases showed no obvious source of infection. In none was a middle ear infection specifically noted, but in such a series accumulated over a period of years, one might justly question the reliability of such observations and only one protocol specifically wrote that the middle ears were negative. The fact that 4 of 5 cases were solitary abscesses may be of some value in attempting interpretation since it is a well accepted fact that while most cerebral abscesses arising by extension from the sinuses or ears are solitary, blood borne abscesses are often multiple. This might be used as additional evidence that these abscesses developed as a result of a relatively low grade bacteremia infecting small infarcts or necroses. In addition the prosector may have failed to observe the usually prominent adhesions and dural reaction at the site of the spread of infection from the middle ear, the mastoid, nasal or venous dural sinuses.

Of the 29 cases in the group of acyanotic heart disease, including those with coarctation of the aorta, patent ductus arteriosis, and interventricular septal defects, the 8 patients with cerebral lesions have been summarized on Table V. The 2 cases with cerebral infarcts occurred in patients without any anatomical defects permitting a venous-arterial shunt. In these 2 children, then, it may be definitely stated that emboli arising on the left side of the heart or its branches or in situ cerebral arterial thrombosis was the cause of the large infarctions. In one patient, having a history of heart failure and hemiplegia, a thrombus was found in a middle cerebral artery. In the other child who awoke from the surgical anesthesia with a hemiplegia and who died 5 days later, a recent thrombus had formed on a peculiar thickened intimal plaque

in the left internal carotid artery. It is obvious then that in these 2 patients paradoxical embolization could not have occurred and existing factors predisposing to thrombus formation, namely, intimal damage and heart failure, were sufficient in the absence of polycythaemia to result in cerebral infarcts in spite of what was probably excellent cerebral blood flow.

It is rather striking, although the relationship is well recognized (26), that of the 10 patients with coarctation of the aorta, 4 had cerebral aneurysms of the circle of Willis, 3 of which had been the cause of death by producing massive sub-arachnoid hemorrhage. One of the patients with a surgically cured patent ductus arteriosis also died of hemorrhage from a congenital aneurysm of the circle of Willis.

SUMMARY

Cerebral lesions of different types occur with greatly increased frequency in patients with congenital heart disease. In patients with cyanotic heart disease, including those having had surgical procedures, cerebral infarctions are particularly common, occurring in 25 of 135 essentially consecutively autopsied cases. Cerebral necroses as a result of the markedly impaired tissue oxygenation without vascular occlusions may account for a relatively small number of cases with microscopic lesions. The majority of the infarcts are the result of vascular occlusions. The important role of polycythaemia in the production of intravascular thromboses as a cause of the infarcts is emphasized and the close similarity in this respect of these patients to cases of polycythaemia vera in adults is discussed. Both arterial and venous cerebral thromboses occur. Whether the thromboses leading to the arterial occlusions usually develop in peripheral veins to reach the cerebral arteries as *paradoxical* emboli through cardiac defects, or form in the cardiac chambers to embolize the brain, or develop in situ in the cerebral arteries is unknown but all mechanisms may occur. Venous thrombi which are seen or are inferred from hemorrhagic infarctions, are more common than arterial occlusions. The severe surgical procedure necessary for the alleviation of these cardiac malformations imposes the additional factors of shock and hemoconcentration on the already increased tendency to thrombosis. Hemorrhagic infarctions are particularly frequent in the immediate postoperative period. The part played by the common attacks of increased cyanosis and fainting in increasing the tendency to thrombosis by further reducing the rate of cerebral blood flow is noted.

Brain abscesses also occur with increased frequency in these patients and the pathogenesis of such lesions is briefly discussed.

Patients with acyanotic heart disease also present many cerebral lesions but these are often of a non-thrombotic origin or, when due to thromboses, obvious causes for such thromboses seem evident although too few patients in this group are available for accurate analysis. A very high incidence of congenital

aneurysms of the circle of Willis in patients with coarctation of the aorta is reported.

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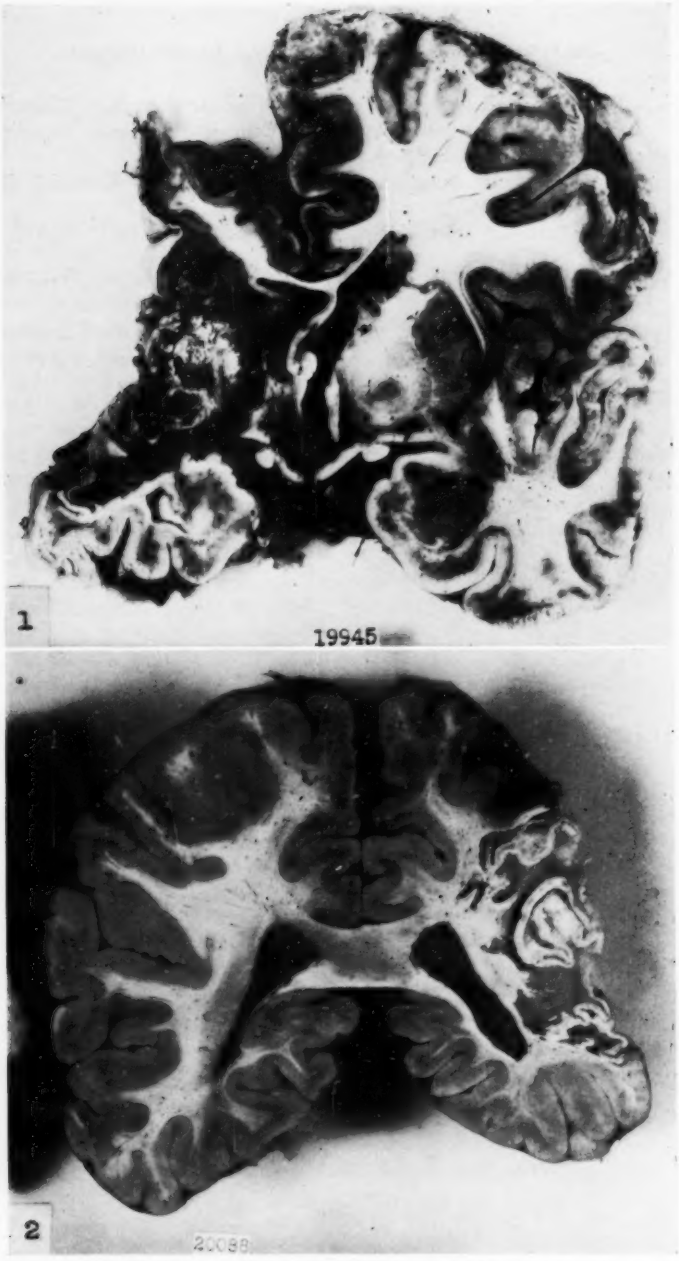


FIG. 1. A massive old infarct of the area supplied by the middle cerebral artery in 3 year old child with tetralogy of Fallot.

FIG. 2. Massive old infarct with recent cortical hemorrhages in 4 year old child with tetralogy of Fallot.

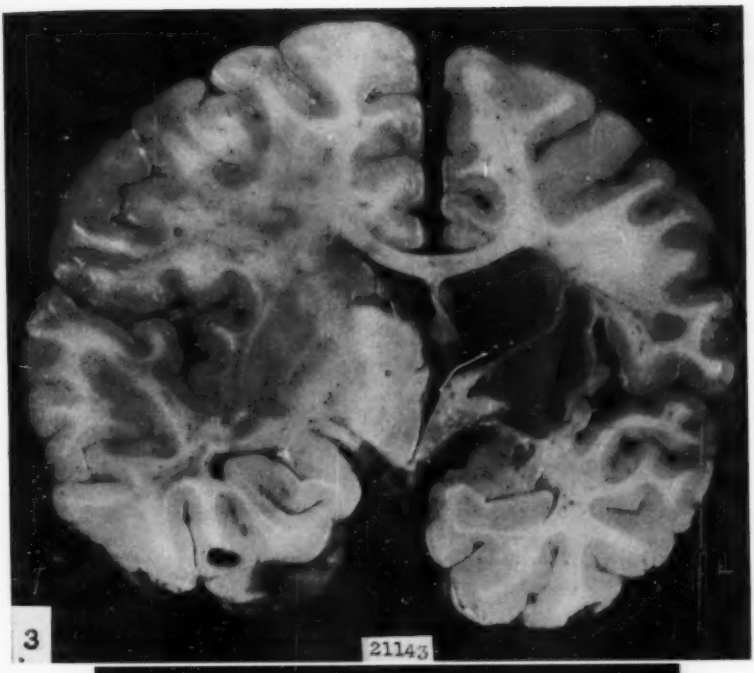
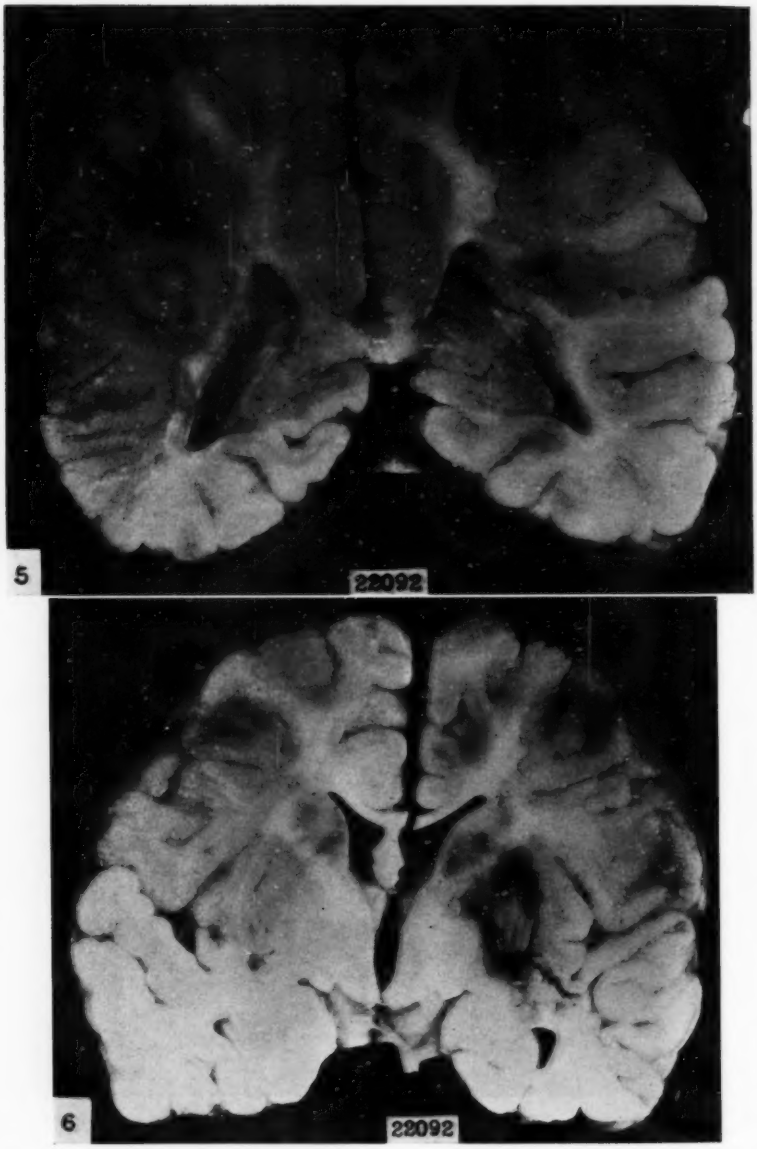


FIG. 3. An old infarct of the right internal capsule and basal ganglia in a child of 9 years with tetralogy of Fallot.

FIG. 4. A massive old infarct from a middle cerebral arterial thrombosis and a recent hemorrhagic infarct from dural sinus and meningeal vein thromboses. This patient, with at trilocular heart and pulmonary atresia had not been operated upon.



FIGS. 5 AND 6. Recent hemorrhagic infarcts from dural sinus and meningeal vein thrombosis in a patient with tetralogy of Fallot, dying only 6 hours after operation.

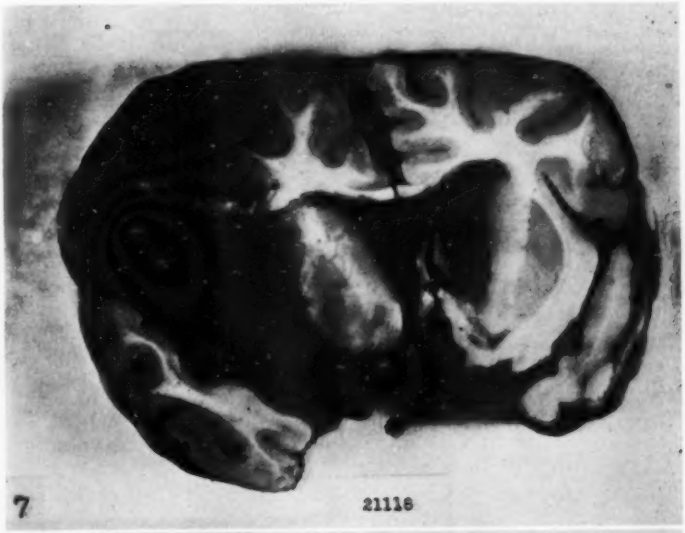


FIG. 7. A massive hemorrhagic infarct of unestablished origin in a 1 year old patient with transposition of the great vessels. No operation.

FIG. 8. Massive hemorrhagic infarction in a 5 months old patient with pulmonary and mitral atresia following dural sinus thrombosis. No operation.

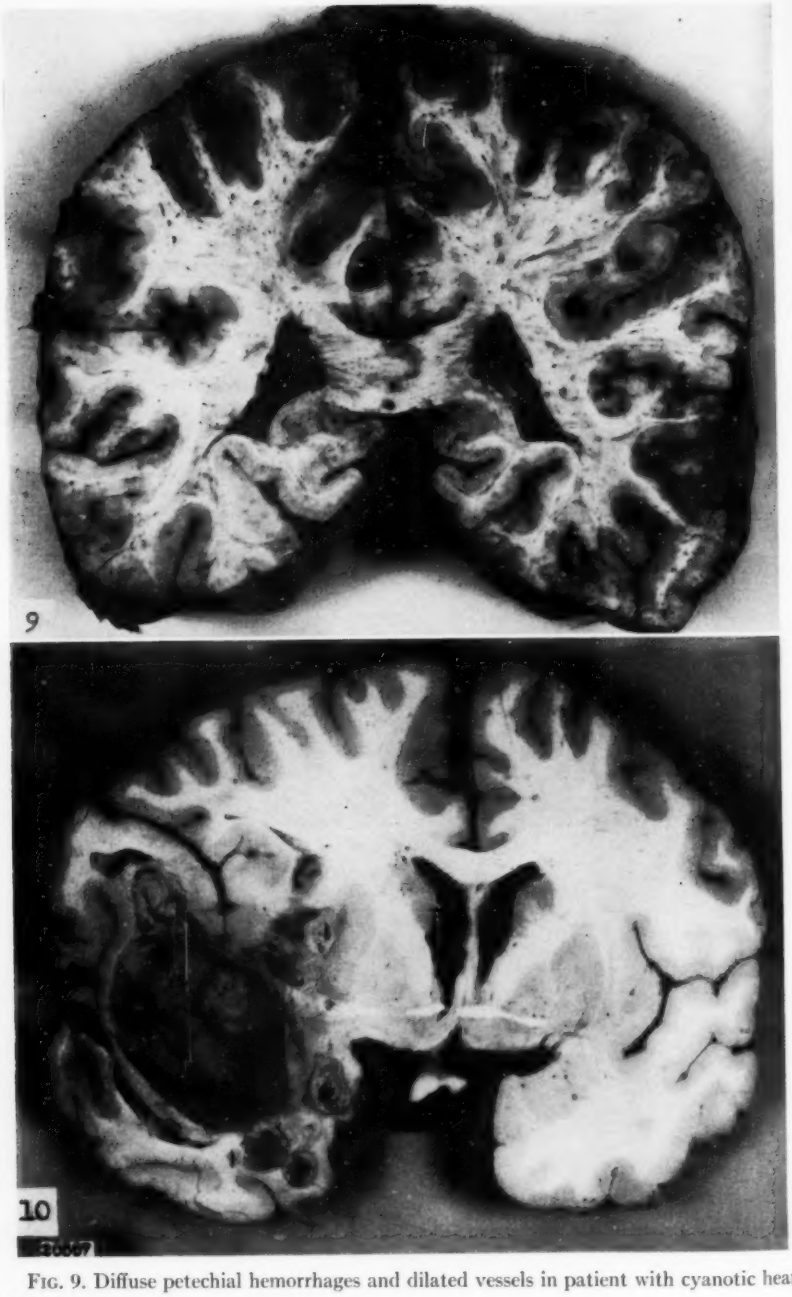


FIG. 9. Diffuse petechial hemorrhages and dilated vessels in patient with cyanotic heart disease.

FIG. 10. Multiple actinomycotic abscesses in 10 year old boy with tetralogy of Fallot.

THE EFFICACY OF AUREOMYCIN IN THE TREATMENT OF PNEUMOCOCCAL LOBAR PNEUMONIA

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Received for publication August 22, 1951

The place of a new chemotherapeutic agent in the treatment of a specific infection for which useful remedies are already available is one that can be determined best by comparative study. To be acceptable, such a new agent should be equally efficacious and no more toxic than drugs currently in use. The potential advantages of an alternative form of treatment may reside in higher therapeutic efficiency, in lower toxicity, in failure to produce untoward reactions in those sensitized previously to other forms of therapy and in a wider range of antimicrobial activity in clinical syndromes caused by a variety of microorganisms identifiable only by laboratory analysis. The usefulness of aureomycin in the therapy of pneumococcal lobar pneumonia has been attested by several published reports (1, 2) and one study comparing the efficacy of aureomycin to penicillin in the treatment of bacterial pneumonia has appeared recently (3). The present study to determine the relative merits of aureomycin and penicillin in the treatment of pneumococcal lobar pneumonia was undertaken to learn if aureomycin would serve as a form of therapy equally satisfactory as those now in use.

METHOD OF STUDY

The study included all patients admitted with the clinical diagnosis of lobar pneumonia to the general medical wards of the Baltimore City Hospital, the Johns Hopkins Hospital, and the U.S. Public Health Service Hospital of Baltimore during the period July 1, 1950 to June 30, 1951. The following laboratory studies were carried out on admission: X-ray of the chest, white blood cell count, blood culture, and a study of the sputum by direct smear, Quellung reaction, culture and mouse inoculation. The assessment of the severity of illness on admission was based upon the objective historical, physical and laboratory findings included in Table I, together with the clinical impression of the physician attending the patient at the time of hospitalization.

The patients were divided into two comparable groups, one receiving aureomycin orally and the other penicillin by intermittent intramuscular injection. All patients whose history number ended in an odd integer received aureomycin (Schedule A) and those with a history number ending in an even integer received intramuscular penicillin (Schedule B).

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Patients on Schedule A received 1 gram of aureomycin[1] orally on admission and 1 gram of aureomycin orally every six hours thereafter. Treatment was continued until the rectal temperature was below 99.6°F for 72 hours. Three patients were treated initially with intravenous aureomycin. Patients on Schedule B received 300,000 units of sodium penicillin G in aqueous solution intramuscularly at the time of admission, at the next 8 o'clock treatment period (A.M. or P.M.) and every 12 hours thereafter, until the rectal temperature was below 99.6°F for 72 hours.

During the course of illness, the following observations were made: rectal temperature every 4 hours; white blood cell count daily until normal, then twice weekly; hemoglobin estimation on days 1 and 2, then twice weekly; urinalysis on days 1, 2, and 3, then twice weekly; X-ray of the chest before discharge or as otherwise indicated.

All patients who were admitted with a clinical diagnosis of pneumococcal lobar pneumonia were included initially in this study. Those in whom the diagnosis could not be substantiated by the isolation of a pneumococcus and by the demonstration of pulmonary consolidation by X-ray were excluded subsequently. Excluded also from the study were six patients whose treatment did not follow the prescribed protocols. Two mildly ill patients and one moderately ill patient with history numbers ending in an odd integer received penicillin instead of aureomycin as set forth in Schedule A. One mildly ill patient and two severely ill patients with history numbers ending in an even integer received penicillin in excess of the amount established in Schedule B. All six patients recovered uneventfully without complications.

RESULTS

One hundred sixteen patients were included in the study, fifty-eight receiving aureomycin (Schedule A) and an equal number penicillin (Schedule B). From the criteria set forth in Table I, the infections were considered to be of moderate and comparable severity in the two groups. The therapeutic response of patients treated with aureomycin (Table II) appeared as satisfactory as the results obtained from treatment with penicillin. One patient was admitted with lobar pneumonia involving the left lung on two occasions to two different hospitals participating in the study. The first infection was caused by pneumococcus type 7 and was treated with aureomycin. The patient's rectal temperature fell from 104°F to 100°F in 28 hours and his leukocyte count returned to normal in four days. He was discharged on the tenth hospital day with nearly complete resolution of the infiltration in the left lower lobe. Seventeen days later he entered the second hospital with lobar pneumonia involving the lower portion of the left upper lobe. Type 16 pneumococci were recovered both from the sputum and blood. On this occasion the patient was treated with penicillin. His rectal temperature fell from 103.6°F to 100°F in 16 hours and his white blood cell count returned to normal on the third day of treatment. Both forms of therapy, therefore, brought about prompt improvement.

Three deaths occurred in this group of patients. Of these one received aureomycin. He was a fifty-four year old white male alcoholic with hypertensive car-

[1] The aureomycin and penicillin used in this study were supplied by Lederle Laboratories Division, American Cyanamid Co. through the courtesy of Dr. Stanton M. Hardy.

diovascular disease who was found unconscious immediately prior to hospitalization. Physical examination gave evidence of shock and of pneumonia involving both lower lobes. The temperature was 101°F, white blood cell count 5,700 and

TABLE I

Analysis of Clinical Data

DATA	PATIENTS GIVEN AUREOMYCIN (SCHEDULE A)		PATIENTS GIVEN I.M. PENICILLIN (SCHEDULE B)		TOTAL	
	No.	%	No.	%	No.	%
Total patients:	58	100.0	58	100.0	116	100.0
Male	41	70.7	47	81.0	88	75.8
Female	17	29.3	11	19.0	28	24.2
Negro	45	77.6	46	79.3	91	78.4
White	13	22.4	12	20.7	25	21.6
Age of patients:						
Under 40 years	34	58.6	35	60.3	69	59.5
40–59 years	19	32.8	18	31.1	37	31.9
60 years and over	5	8.6	5	8.6	10	8.6
Severity of disease:						
Mild	25	43.1	29	50.0	54	46.5
Moderate	22	37.9	15	25.8	37	31.9
Severe	8	13.8	14	24.2	22	19.0
Critical	3	5.2	0	0.0	3	2.6
Duration of illness before therapy:						
1 or 2 days	27	46.5	19	32.8	46	39.6
3 or 4 days	17	29.3	21	36.1	38	32.8
5 or 6 days	7	12.1	11	19.0	18	15.5
Over 6 days	7	12.1	7	12.1	14	12.1
Indications of severity:						
Bacteremia	14	24.2	17	29.3	31	26.7
Multilobar involvement	15	25.9	17	29.3	32	27.6
Leukocytes less than 8,000 per cu.mm.	5	8.6	7	12.1	12	10.3
Shock	2	3.4	1	1.7	3	2.6
Disorientation	4	6.9	9	15.5	13	11.2
Jaundice	3	5.2	0	0.0	3	2.6
Alcoholism	19	32.8	17	29.3	36	31.0
Other complicating diseases*	14	24.2	18	31.0	32	27.6
Pneumococcal types:						
1–8	40	69.0	36	62.2	76	65.5
Higher types	18	31.0	20	34.4	38	32.8
Untyped	0	0.0	2	3.4	2	1.7
Patients receiving prior treatment	0	0.0	1	1.7	1	0.9

* Cardiac failure, diabetes, liver disease, others.

pneumococcus type 18 was recovered from the sputum though blood culture was sterile. The patient was given one gram of aureomycin intravenously but failed to respond and died eight hours after admission. Autopsy showed pneumonia involving all pulmonary lobes but the left upper. Two patients

treated with penicillin expired. One was a forty-three year old Negro male admitted in a disoriented state on the fourth day of illness with lobar pneumonia of the right upper and left lower lobes due to pneumococcus type 3. Blood culture was sterile and the leukocyte count was 12,000. The patient was treated with penicillin and his temperature fell from 103°F to 100.6°F twelve hours following admission. An hour before death the patient's general

TABLE II

Results of Treatment

DATA	PATIENTS GIVEN AUREOMYCIN (SCHEDULE A)		PATIENTS GIVEN I.M. PENICILLIN (SCHEDULE B)		TOTAL	
	No.	%	No.	%	No.	%
Total Patients	58	100	58	100	116	100
Duration of fever following start of therapy						
1 day or less	17	29.3	23	39.6	40	34.5
2 days	20	34.4	16	27.6	36	31.0
3 days	6	10.4	3	5.2	9	7.8
4 days or more	15	25.9	16	27.6	31	26.7
Duration of WBC greater than 10,000*						
3 days or less	25	43.1	27	46.5	52	45.2
4–6 days	18	31.0	9	15.5	27	23.2
7 days or more	10	17.2	11	19.0	29	25.0
Complications	4	6.8	7	12.1	11	9.5
Deaths	1	1.7	2	3.4	3	2.6

* Sixteen patients did not have a white blood cell count as high as 10,000 per cu. mm. during their illness.

TABLE III

Comparison of Intestinal Activity During Treatment with Aureomycin and Penicillin

	AUREOMYCIN TREATED (33)		PENICILLIN TREATED (36)	
	No.	%	No.	%
More than 4 bowel movements a day	19	57.5	9	25.0
No spontaneous bowel movement for 48 hours	9	27.3	18	50.0
Average number of stools per day	2.1		1.1	

condition appeared worse and he expired suddenly, apparently in cardiovascular collapse. At autopsy, the clinical impression of pneumonia involving the right upper and left lower lobes was confirmed and viable type 3 pneumococci were recovered from the lungs. No contributory factors to account for the patient's demise were noted and the case must be considered a therapeutic failure. The third death occurred in a sixty-five year old colored female diabetic with arteriosclerotic heart disease admitted with lobar pneumonia of the right upper and middle lobes and bacteremia due to pneumococcus type 9. She was treated with

penicillin and her temperature fell from 103.4°F to 100°F forty hours following hospitalization. Blood cultures taken 24 and 48 hours after admission showed no pneumococci. On the seventh hospital day, the patient's temperature rose again to 103.2°F and the dose of penicillin was increased to 2,400,000 units daily. She was thought to have partial collapse of her right upper lobe and was bronchoscoped with subsequent improvement. On the tenth hospital day the patient coughed and suddenly expired. Autopsy revealed residual consolidation in the right upper lobe with abscess formation, atelectasis of the right lower lobe and embolization of the left pulmonary artery which was doubtless responsible for the patient's sudden exitus.

The schedule of treatment prescribed by the protocol was abandoned in three patients treated initially with aureomycin and in four persons treated at the start with penicillin. Of the patients receiving aureomycin, one was a sixty-eight year old colored male with lobar pneumonia of the right upper lobe and bacteremia due to pneumococcus type 1. He seemed to respond well to aureomycin by mouth but bacteremia persisted for twenty-four hours and he developed subsequently purulent arthritis of the left shoulder and sternoclavicular joints from which joints, however, no pneumococci could be recovered. His course was complicated further by delayed resolution of the pneumonic process and, on the fifteenth hospital day, treatment with penicillin was instituted without any noteworthy alteration of his clinical course. At the time of discharge from the hospital, the patient had extensive fibrotic changes in his right upper lobe, some of which alterations may have antedated the onset of pneumonia. A second patient treated initially with aureomycin was a fifty-nine year old colored female with advanced hypertensive cardiovascular renal disease who entered the hospital in a semi-stuporous state with lobar pneumonia of the left upper lobe and bacteremia due to pneumococcus type 19. Therapy with intravenous aureomycin resulted in prompt defervescence and sterilization of the blood stream within twelve hours. The persistence of the patient's semi-stuporous state necessitated continuation of intravenous therapy for three days by which time thrombosis of peripheral veins resulting from the administration of aureomycin precluded maintenance of this form of therapy. Treatment with penicillin intramuscularly was begun, therefore, after the patient had been afebrile for forty-eight hours and she recovered ultimately. The third patient who was treated first with aureomycin was a seventy-seven year old white male with lymphatic leukemia who became ill with lobar pneumonia of the right upper lobe due to pneumococcus type 33. On treatment with aureomycin, his temperature fell from 105°F on admission to normal levels on the third hospital day. On the fourth hospital day, the patient's temperature rose to 102.4°F and he vomited. Because of gastrointestinal irritability and granulocytopenia, it was felt advisable to treat the patient with penicillin. His fever disappeared promptly and he recovered uneventfully. Of the patients' treated initially with penicillin whose therapy was altered, the

first was a forty-eight year old colored male alcoholic with hepatic cirrhosis hospitalized for lobar pneumonia of the left lower lobe and bacteremia due to pneumococcus type 1. His defervescence was slow despite sterilization of the blood stream and on the sixth hospital day a pericardial friction rub was detected together with electrocardiographic changes compatible with pericarditis. Because of these findings and the obtaining of a questionable history of previous hypersensitivity to penicillin, the patient was treated with aureomycin after the fifth hospital day. His temperature fell gradually by lysis and he recovered satisfactorily. A second patient with lobar pneumonia and bacteremia due to pneumococcus type 1 was treated with penicillin and became afebrile in three days. On the fifth day of treatment his temperature rose again to 103°F and his sputum was found to contain at this time large numbers of *Aerobacter aerogenes*. Therapy was supplemented with sulfadiazine and the patient recovered without untoward event. A thirty-eight year old colored male alcoholic with evidence of phlebothrombosis of the left leg was hospitalized with lobar pneumonia of the left upper lobe due to pneumococcus type 7 and treated with penicillin. On the sixth hospital day he had delirium tremens accompanied by a transitory rise in temperature and was sedated heavily. On the fourteenth day of treatment he again had fever accompanied by signs of infiltration in the right middle lobe and a small amount of pleural fluid. It was uncertain whether or not the patient had aspiration pneumonia consequent to his delirium tremens or a pulmonary infarction. The sputum at this time showed normal flora. He was treated at this juncture with aureomycin for five days and made a satisfactory recovery. A fourth patient treated with penicillin for lobar pneumonia of the right middle and lower lobes and bacteremia due to pneumococcus type 5 responded rather slowly to therapy and, on the eighth hospital day, the dose of penicillin was quadrupled. This change in dosage did not appear to accelerate the patient's progress to ultimate recovery.

Complications were infrequent in patients treated either with aureomycin or with penicillin. Resolution of the pneumonic process was delayed beyond three weeks in four patients receiving aureomycin, one of whom developed purulent arthritis, and in seven patients treated with penicillin two of whom developed pulmonary cavitation and one fibrinous pericarditis.

Toxic reactions to either drug were uncommon. One of the three patients receiving aureomycin intravenously suffered multiple venous thromboses at the sites of injection. No cases of secondary moniliasis, rash or fever attributable to this drug were recognized. Nausea and vomiting caused by aureomycin were considerations for abandoning the use of this drug in but one instance. As indicated in Table III, of thirty-three patients treated with aureomycin, nearly three-fifths had on at least one occasion more than four stools in one day while receiving the drug whereas but a quarter of a comparable group of patients treated with penicillin manifested similar intestinal hypermotility. On the other hand, half of this group of patients treated with penicillin failed to have a spontaneous bowel movement for a forty-eight hour period during

the acute phase of illness whereas evidence of obstipation was manifested by little more than a quarter of those treated with aureomycin. No evidence of hypersensitivity was noted in any patient treated with aureomycin. Two patients receiving penicillin developed morbilliform eruptions and fever.

DISCUSSION

The results of this study indicate that aureomycin is a satisfactory drug for the treatment of pneumococcal lobar pneumonia and are in essential agreement with those published previously (1, 2, 3). Aureomycin compares favorably with penicillin in its efficacy and lack of toxicity and may be administered orally to all but the most seriously ill. Diarrhoea may occasionally prove a troublesome complication of treatment with aureomycin but can be controlled in some measure by administration of the drug after meals or with milk. The use of aluminum hydroxide preparations should be avoided, however, as they lessen appreciably absorption of the drug from the gastrointestinal tract (4, 5). The stimulant effect of aureomycin upon intestinal motility may not be altogether without benefit for it tends to diminish the development of obstipation and abdominal distention which may prove, at times, a distressing complication of pneumococcal pneumonia. In the management of patients with pneumococcal lobar pneumonia who manifest hypersensitivity to penicillin, aureomycin provides an acceptable alternative form of therapy. In addition, because aureomycin inhibits a wider range of bacterial species than does penicillin, it may be preferable to the latter drug in the treatment of acute pneumonia when laboratory facilities for establishing an aetiologic diagnosis are unavailable.

SUMMARY

The efficacy of aureomycin in the treatment of pneumococcal lobar pneumonia has been assessed by comparing the results of treatment with this drug to those obtained from the administration of penicillin.

In agreement with the results of others, aureomycin has been found to be a satisfactory drug for the treatment of pneumococcal lobar pneumonia.

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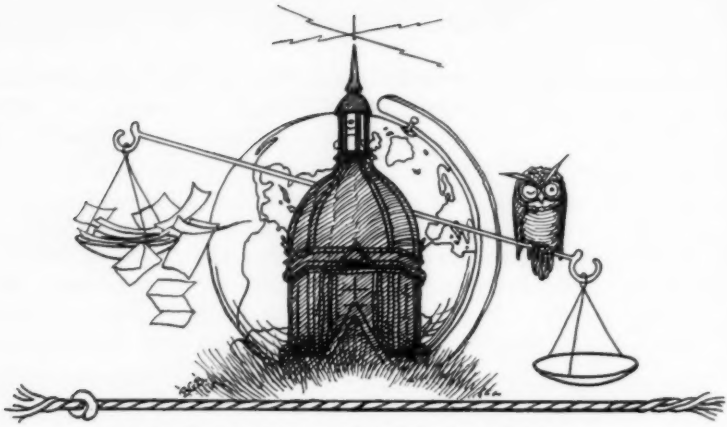

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

The Collected Papers of Adolf Meyer. Four Volume Set $30.00. Edited by EUNICE WINTERS. Vol. II, Psychiatry. With an Introduction by Sir David K. Henderson, M.D. 674 pp. *The Johns Hopkins Press, Baltimore, Md.*

This second in a projected series of four volumes of Dr. Meyer's collected papers follows a volume of his neurological contributions and contains his papers on psychiatry in the narrower sense, that is, mental hospitals and mental disease. Papers on medical teaching and mental hygiene are promised in subsequent volumes. The appearance of these volumes rescues Meyer's immense and still very pertinent contributions from the threatened oblivion of widely scattered journals and makes them available in an organized, usable form.

As with the first volume, the format is pleasing, the editing skillful and the index excellent. Sir David K. Henderson, the first resident of Phipps, contributes in his introduction an impressive evaluation of Meyer and his work. The wide diversity of Meyer's psychiatric interests presents great problems for an editor who is unwilling to fall back on a merely chronological arrangement. The organization of this volume cannot prevent some overlapping and repetition but fortunately Meyer's ideas gain by reiteration.

The book is introduced by Meyer's Presidential Address to the American Psychiatric Association in 1928, a wise choice since it touches on most of the points which subsequent papers develop in detail. There follows a large section entitled "Organization of Medical Work," consisting largely of selections from Meyer's annual reports at Worcester State Hospital and the New York State Pathological Institute, and his plans for the Phipps Clinic. Contrary to what might be expected, these papers are highly rewarding. The problems of mental hospitals such as understaffing, overcrowding, demoralization of medical staffs, disproportionate concern with administrative matters to the neglect of medical work with patients, unfortunately have shown little change in the past fifty years, and Meyer's concrete remedial proposals are as cogent as ever. These papers too offer a unique sense of the man at work—how he grapples with a highly complex situation, grasps it in its overall aspects and in detail, decides on the most important things to be done and then fights for them year after year, patiently, good-humoredly, but uncompromisingly and with inex-

haustible energy, gradually making headway. Never is there a hint of discouragement or of anything but constructive criticism, and only by reading between the lines can the reader feel the indifference, inertia and obstructionism he had to battle. His plans for the Phipps Clinic, which still serves as a model for any university psychiatric clinic, appear to have been realized except in one interesting respect. Meyer believed that to understand mental illness one had to study the patient in his actual environment, and to this end proposed to admit free all patients from one city district and to study intensively their relations to their families and general socio-economic environment over a long period of time. In this he showed his appreciation of the importance of sociological forces in mental illness, something which is just now being emphasized. Unfortunately funds for such a plan were lacking, and all that materialized was Dr. C. Macfie Campbell's psychiatric survey of the Eastern Health District.

The middle third of the volume entitled "Early Medical Formulations" contains miscellaneous papers, some of great interest. Among these are two exhaustive, critical evaluations of the leading systematic psychiatries of the early twentieth century—those of Wernicke, Kraepelin, and Ziehen—which remain valuable as summaries; a beautiful short clinical paper on "Arteriosclerosis and Mental Disease," and a brief paper, "On Some Terminal Diseases in Melancholia," which in a way epitomizes all that Meyer stood for. In it he extracts from autopsy findings both a plea for better nursing of mental patients and the delineation of one of his main contributions to neuropathology, "central neuritis," thus vividly demonstrating his capacity for making practical use of whatever came to his hand.

The bulk of the last third of the volume contains Meyer's classical formulations of dementia praecox as habit disorganization to be treated by re-education and habit training, and his unsurpassed paper on the treatment of paranoic and paranoid states, perhaps the high spot of the book in its grasp of a very difficult problem and its stimulating suggestions for dealing with it.

This is followed by a surprisingly brief section on affective disorders, consisting chiefly of definitions of terms for Baldwin's Dictionary of Philosophy and Psychology. Meyer sees elation and depression not as clinical entities but as manifestations of many diverse psychic disorders, an insight now generally accepted.

The final section, "Psychopathology and Psychodynamics," contains a few miscellaneous papers which give Meyer's broader formulations, especially his non-dogmatic functional, pluralistic approach to the problems of human nature, most clearly developed in "The Problems of Mental Reaction Types, Mental Causes and Diseases."

Despite the diversity of material to which Meyer bent his formidable energies, he maintained throughout a consistent viewpoint and way of work. This is summed up in his phrase "a love of conscience concerning facts," (104) wherever and in whatever guise they appear and regardless of whether they fit theoretical schemes; and the use of such facts to suggest and guide concrete action: "The most essential achievement is not the erection of a word-palace of logic or of description, but the enlargement of our command of action." (597) The harmony of this viewpoint with the American philosophical climate probably accounts both for his enthusiastic acceptance of this country and the extent of his influence here. Consistent with this outlook he approached each new problem with an attitude of unbiased, careful inquiry, mastered it, and then singled out points for action. He had a keen interest in any investigative method which showed promise and did not allow personal bias to cause him to slight anything of potential usefulness. Thus, despite expressed skepticism, he made exhaustive anthropometric measurements to detect so-called physical signs of degeneration. Whether charting the morass of a state hospital system, tracking his way through the conceptual jungles of a Wernicke, or summing up the state of American psychiatry, he first

presents in masterful fashion the data as he sees them and only then ventures his comments and suggestions. He was impatient of theory not firmly grounded in facts ("Definitions of words are always welcome; but they should not claim to be definitions of facts unless they can be proved to deserve it," 513), continually urged presentation of concrete case material, and formulated psychotherapy as "not talk or thought alone but the *doing of* things." (586)

It can be argued that Meyer's almost religious veneration for facts in all their multiplicity prevented him from pushing through to concise theoretical formulations which, after all, are necessary to guide the selection and ordering of facts. For Meyer a sufficient guiding principle was relevance for action or further investigation, and his great intellectual capacity enabled him to assimilate masses of facts without losing his bearings, but most of us need clearer principles of selectivity. Nevertheless his viewpoint is basically the only sound one and remains a valuable antidote and corrective in a field as fad- and theory-ridden as psychiatry.

This volume will repay careful study by psychiatrists for its soundness of viewpoint, its cogent practical suggestions for handling a wide range of problems from mental hospital organization to the treatment of schizophrenics, its impressive summaries of psychiatric works unjustly neglected today, and its clinical insights. One leaves it with renewed respect for Adolf Meyer as a dynamic, far-seeing administrator, educator, clinician and philosopher in psychiatry.

JOHN C. WHITEHORN AND JEROME FRANK

Clinical Tropical Medicine. Edited by R. B. H. GRADWOHL, LOUIS BENITEZ SOTO, AND OSCAR FELSENFELD. 1647 pp., $22.50. *The C. V. Mosby Co., St. Louis, Mo.*

It is well known that the term "Tropical Medicine" no longer includes only diseases found in the tropics. Many of them occur in cold climates. Present day rapid communication brings tropical and nontropical areas so close together that the medical practitioners in nontropical countries should be more familiar with exotic diseases. World War II gave the medical profession a great opportunity to study in detail many "tropical diseases" which has increased our knowledge. This book compiles such up-to-date information.

This book was written by 57 contributors, largely Pan-American authors, leaders in various fields of tropical medicine. Although the various authors had their own freedom of expression, they followed a general pattern of presentation of the diseases e.g. definition, history, epidemiology, pathology, clinical picture, diagnosis, prognosis, treatment, prevention and bibliography. Different authors stressed different aspects.

The book is divided into many sections: protozoa, viruses, bacteria, rickettsia, helminths, fungi, arthropods, animal poisons and nutritional deficiencies. It also contains a few chapters on therapeutics, laboratory methods, hygiene and organization of preventive medicine in the tropics. There are 73 chapters in all which thus cover almost all subjects known to be related to tropical medicine.

A huge book like this one must have taken several years in preparation. Thus the materials and literature are mainly dated prior to 1948. A number of discoveries in tropical medicine have been since added. In the chapters on malaria, although one author gave the reference and cited Shortt's discovery of the pre-erythrocytic stages of plasmodium in the human liver, the illustrated plates do not include this possibility and still indicate the previous concepts of direct introduction of the sporozoites into the red blood cells after inoculation by the infected mosquito. As to therapeutics, the successful application of antibiotics to treat the rickettsial diseases, typhoid fever and amoebiasis etc. could not be elaborated when the book was written. However, the editors have added many footnotes in various chapters referring to these antibiotic agents in therapy.

In general, this is probably the best and most complete text book on tropical medicine today. It is a valuable addition to the library of those who are interested in tropical diseases.

C. L.

Post-Graduate Lectures on Orthopedic Diagnosis and Indications. Volume II. By ARTHUR STEINDLER. 208 pp., $6.00. *Charles C. Thomas, Springfield, Ill.*

In Volume II of his Post-Graduate Lectures, Steindler extends his coverage of orthopedic subjects. The book is divided into two sections, the first on paralytic disabilities and the second on static disabilities. The lectures on paralysis discuss (a) anterior poliomyelitis, including the disease proper, residual deformities and methods of treatment, and (b) spastic paralysis. Under the heading of static disabilities there are presented the following subjects, —low back pain, idiopathic scoliosis, internal derangements of the knee, and static deformities of the ankle and foot from flatfoot to ingrown toenail.

This constitutes a great deal of material for approximately 180 pages and properly makes one look askance at the claim on the jacket, "Answers all questions." There is, however, a remarkable mass of subject matter packed within these pages. This is accomplished by the use of an overall outline form that permits discrete and terse statements to fall into their logical place without the need of transitional sentences to give continuity. In effect, it permits the advanced student of orthopedics to survey a large amount of well correlated information in a minimum of time, a quality that will prove of value to the busy orthopedist.

W. N.

BOOKS RECEIVED FOR REVIEW

Clinical and Roentgenologic Evaluation of the Pelvis in Obstetrics. (American Monograph Series). By HOWARD C. MOLOY. 119 pp., $2.50. *W. B. Saunders Co., Philadelphia, Pa.*

A Color Atlas of Morphologic Hematology. By GENEVA A. DALAND. Edited by Thomas Hale Ham. Illustrations by Etta Piotti. 74 pp., $5.00. *Harvard University Press, Cambridge, Mass.*

Fractures, Dislocations, and Sprains. 5th edition. By JOHN ALBERT KEY AND H. EARLE CONWELL. 1232 pp., $16.00. *The C. V. Mosby Co., St. Louis, Mo.*

Frontal Lobotomy and Affective Behavior. By JOHN F. FULTON. 160 pp., $3.00. *W. W. Norton & Co., New York.*

Labelled Atoms. (Sigma Series). By RAYMOND GLASCOCK. 227 pp., $1.25. *Interscience Publishers, Inc., New York.*

Leitfaden Der Laparoskopie Und Gastroskopie. By H. KALK AND W. W. BRUHL. 158 pp., Ganzleinen DM 27. *Georg Thieme Verlag, Stuttgart, Germany.*

Metabolic Methods. Clinical Procedures in the Study of Metabolic Functions. By C. FRANK CONSOLAZIO, ROBERT E. JOHNSON, AND EVELYN MAREK. 471 pp., $6.75. *The C. V. Mosby Co., St. Louis, Mo.*

Primary Anatomy. By H. A. CATES. 344 pp., $6.00. *Williams & Wilkins Co., Baltimore, Md.*

Über Die Röntgenologischen Darstellungsmöglichkeiten Des Weiblichen Genitalapparates Mit Hilfe Von Jodol Und Jodsöl. By J. ERBSLOH. 74 pp., Kartoniert DM 16.80. *Georg Thieme Verlag, Stuttgart, Germany.*